DNA Basics

: Biochemistry,Structure, Dynamics, Molecular Modeling and Technologies

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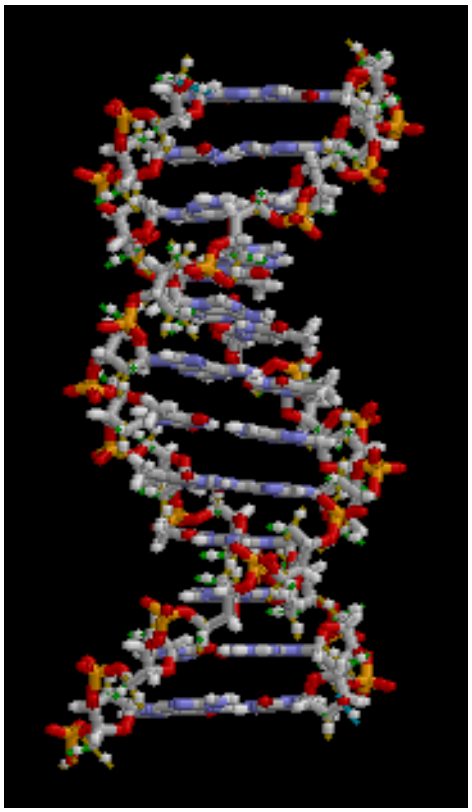
DNA Biochemistry and Structure

DNA

Deoxyribonucleic acid (**DNA**) is a nucleic acid that contains the genetic instructions used in the development and functioning of all known living organisms and some viruses. The main role of DNA molecules is the long-term storage of information. DNA is often compared to a set of blueprints or a recipe, or a code, since it contains the instructions needed to construct other components of cells, such as proteins and RNA molecules. The DNA segments that carry this genetic information are called genes, but other DNA sequences have structural purposes, or are involved in regulating the use of this genetic information.



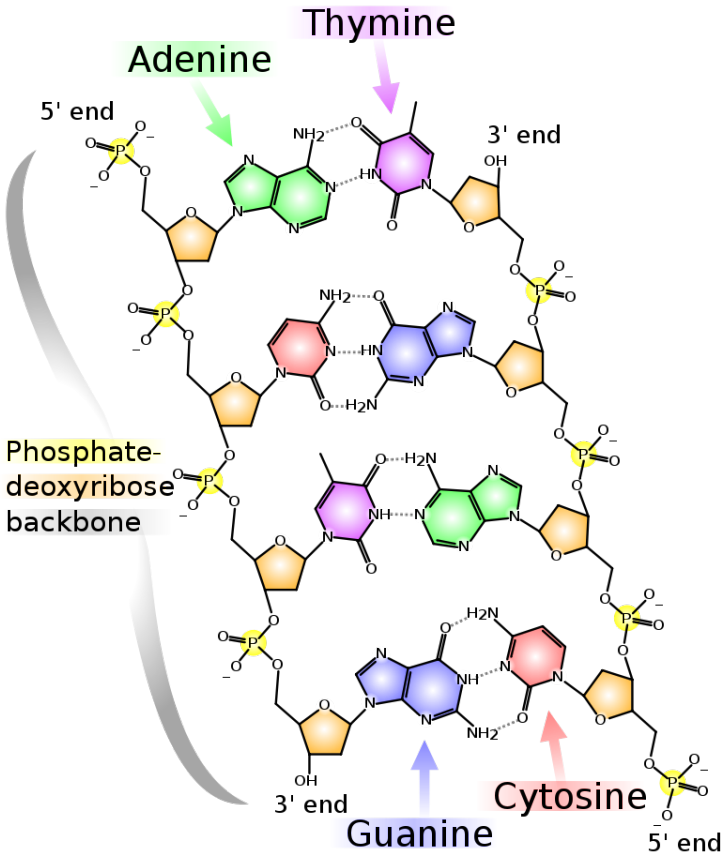
The structure of part of a DNA double helix

Chemically, DNA consists of two long polymers of simple units called nucleotides, with backbones made of sugars and phosphate groups joined by ester bonds. These two strands run in opposite directions to each other and are therefore anti-parallel. Attached to each sugar is one of four types of molecules called bases. It is the sequence of these four bases along the backbone that encodes information. This information is read using the genetic code, which specifies the sequence of the amino acids within proteins. The code is read by copying stretches of DNA into the related nucleic acid RNA, in a process called transcription.

Within cells, DNA is organized into structures called chromosomes. These chromosomes are duplicated before cells divide, in a process called DNA replication. Eukaryotic organisms (animals, plants, fungi, and protists) store most of their DNA inside the cell nucleus and some of their DNA in the mitochondria. Prokaryotes (bacteria and archaea) however, store their DNA in the cell's cytoplasm. Within the chromosomes, chromatin proteins such as histones compact and organize DNA. These compact structures guide the interactions between DNA and other proteins, helping control which parts of the DNA are transcribed.

Properties

DNA is a long polymer made from repeating units called nucleotides.[1] [2] [3] These nucleotides are adenine (A), guanine (G), cytosine (C) and thymine (T). In the related nucleic acid RNA, thymine is replaced by uracil (U). These nucleotides can be classified into two groups: purines (adenine and guanine) and pyrimidines (thymine and cytosine).



The chemical structure of DNA. Hydrogen bonds are shown as dotted lines.

The DNA chain is 22 to 26 Ångströms wide (2.2 to 2.6 nanometres), and one nucleotide unit is 3.3 Å (0.33 nm) long.[4] Although each individual repeating unit is very small, DNA polymers can be very large molecules containing millions of nucleotides. For instance, the largest human chromosome, chromosome number 1, is approximately 220 million base pairs long.[5]

In living organisms, DNA does not usually exist as a single molecule, but instead as a pair of molecules that are held tightly together.[6] [7] These two long strands entwine like vines, in the shape of a double helix. The nucleotide repeats contain both the segment of the backbone of the molecule, which holds the chain together, and a base, which interacts with the other DNA strand in the helix. In general, a base linked to a sugar is called a nucleoside and a base linked to a sugar and one or more phosphate groups is called a nucleotide. If multiple nucleotides are linked together, as in DNA, this polymer is called a polynucleotide.[8]

The backbone of the DNA strand is made from alternating phosphate and sugar residues.[9] The sugar in DNA is 2-deoxyribose, which is a pentose (five-carbon) sugar. The sugars are joined together by phosphate groups that form phosphodiester bonds between the third and fifth carbon atoms of adjacent sugar rings. These asymmetric bonds mean a strand of DNA has a direction. In a double helix the direction of the nucleotides in one strand is opposite to their direction in the other strand. This arrangement of DNA strands is called antiparallel. The asymmetric ends of DNA strands are referred to as the 5′ (*five prime*) and 3′ (*three prime*) ends, with the 5' end being that with a terminal phosphate group and the 3' end that with a terminal hydroxyl group. One of the major differences between DNA and RNA is the sugar, with 2-deoxyribose being replaced by the alternative pentose sugar

ribose in RNA.[7]

The DNA double helix is stabilized by hydrogen bonds between the bases attached to the two strands. The four bases found in DNA are adenine (abbreviated A), cytosine (C), guanine (G) and thymine (T). These four bases are attached to the sugar/phosphate to form the complete nucleotide, as shown for adenosine monophosphate.

These bases are classified into two types; adenine and guanine are fused five- and six-membered heterocyclic compounds called purines, while cytosine and thymine are six-membered rings called pyrimidines.[7] A fifth pyrimidine base, called uracil (U), usually takes the place of thymine in RNA and differs from thymine by lacking a methyl group on its ring. Uracil is not usually found in DNA, occurring only as a breakdown product of cytosine.

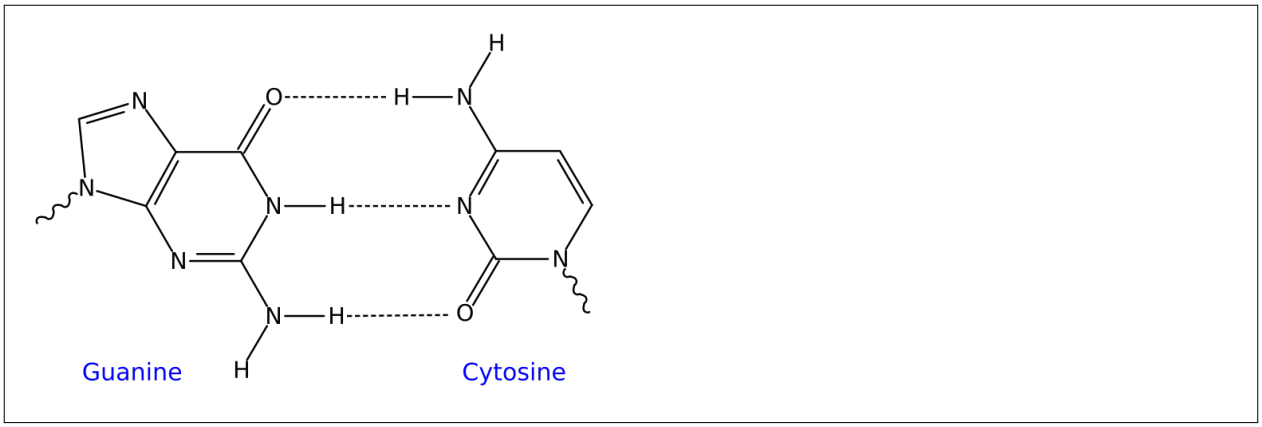
Grooves

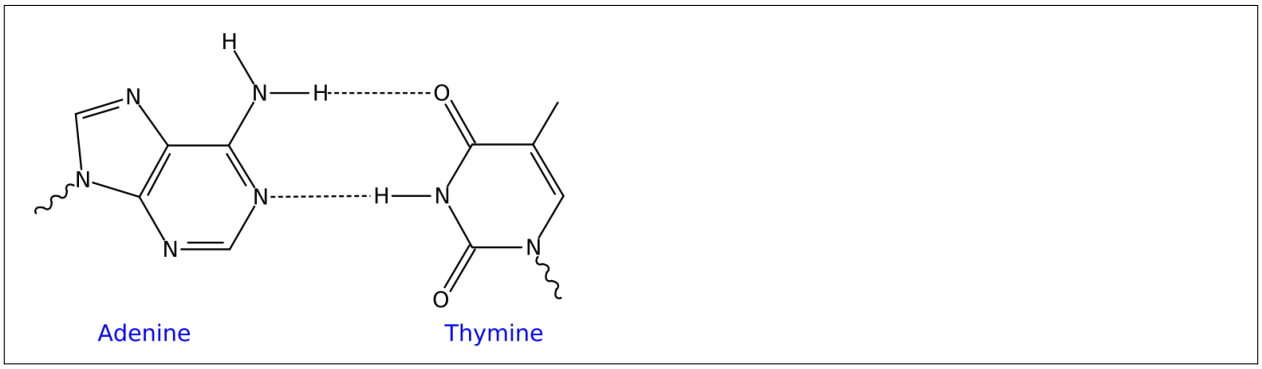
Twin helical strands form the DNA backbone. Another double helix may be found by tracing the spaces, or grooves, between the strands. These voids are adjacent to the base pairs and may provide a binding site. As the strands are not directly opposite each other, the grooves are unequally sized. One groove, the major groove, is 22 Å wide and the other, the minor groove, is 12 Å wide.[11] The narrowness of the minor groove means that the edges of the bases are more accessible in the major groove. As a result, proteins like transcription factors that can bind to specific sequences in double-stranded DNA usually make contacts to the sides of the bases exposed in the major groove.[12] This situation varies in unusual conformations of DNA within the cell *(see below)*, but the major and minor grooves are always named to reflect the differences in size that would be seen if the DNA is twisted back into the ordinary B form.

Structure of a section of DNA. The bases lie horizontally between the two spiraling strands.[10] Animated version at File:DNA orbit animated.gif - over 3 megabytes.

Base pairing

Each type of base on one strand forms a bond with just one type of base on the other strand. This is called complementary base pairing. Here, purines form hydrogen bonds to pyrimidines, with A bonding only to T, and C bonding only to G. This arrangement of two nucleotides binding together across the double helix is called a base pair. As hydrogen bonds are not covalent, they can be broken and rejoined relatively easily. The two strands of DNA in a double helix can therefore be pulled apart like a zipper, either by a mechanical force or high temperature.[13] As a result of this complementarity, all the information in the double-stranded sequence of a DNA helix is duplicated on each strand, which is vital in DNA replication. Indeed, this reversible and specific interaction between complementary base pairs is critical for all the functions of DNA in living organisms.[2]





Top, a **GC** base pair with three hydrogen bonds. Bottom, an **AT** base pair with two hydrogen bonds. Non-covalent hydrogen bonds between the pairs are shown as dashed lines.

The two types of base pairs form different numbers of hydrogen bonds, AT forming two hydrogen bonds, and GC forming three hydrogen bonds (see figures, left). DNA with high GC-content is more stable than DNA with low GC-content, but contrary to popular belief, this is not due to the extra hydrogen bond of a GC basepair but rather the contribution of stacking interactions (hydrogen bonding merely provides specificity of the pairing, not stability).[14] As a result, it is both the percentage of GC base pairs and the overall length of a DNA double helix that determine the strength of the association between the two strands of DNA. Long DNA helices with a high GC content have stronger-interacting strands, while short helices with high AT content have weaker-interacting strands.[15] In biology, parts of the DNA double helix that need to separate easily, such as the TATAAT Pribnow box in some promoters, tend to have a high AT content, making the strands easier to pull apart.[16] In the laboratory, the strength of this interaction can be measured by finding the temperature required to break the hydrogen bonds, their melting temperature (also called T_m value). When all the base pairs in a DNA double helix melt, the strands separate and exist in solution as two entirely independent molecules. These single-stranded DNA molecules have no single common shape, but some conformations are more stable than others.[17]

Sense and antisense

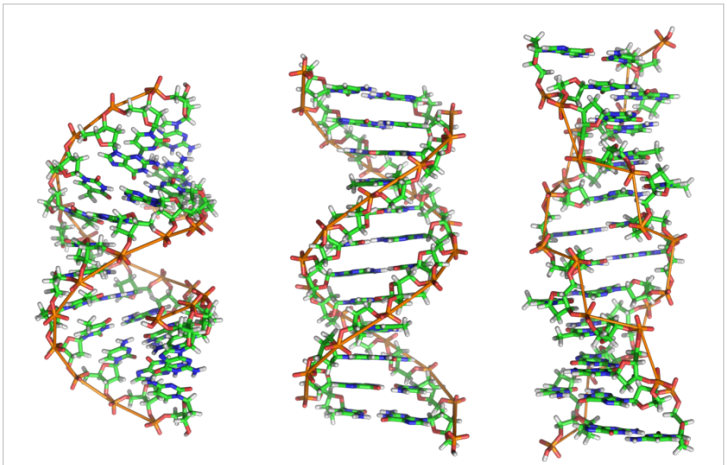
A DNA sequence is called "sense" if its sequence is the same as that of a messenger RNA copy that is translated into protein.[18] The sequence on the opposite strand is called the "antisense" sequence. Both sense and antisense sequences can exist on different parts of the same strand of DNA (i.e. both strands contain both sense and antisense sequences). In both prokaryotes and eukaryotes, antisense RNA sequences are produced, but the functions of these RNAs are not entirely clear.[19] One proposal is that antisense RNAs are involved in regulating gene expression through RNA-RNA base pairing.[20]

A few DNA sequences in prokaryotes and eukaryotes, and more in plasmids and viruses, blur the distinction between sense and antisense strands by having overlapping genes.[21] In these cases, some DNA sequences do double duty, encoding one protein when read along one strand, and a second protein when read in the opposite direction along the other strand. In bacteria, this overlap may be involved in the regulation of gene transcription,[22] while in viruses, overlapping genes increase the amount of information that can be encoded within the small viral genome.[23]

Supercoiling

DNA can be twisted like a rope in a process called DNA supercoiling. With DNA in its "relaxed" state, a strand usually circles the axis of the double helix once every 10.4 base pairs, but if the DNA is twisted the strands become more tightly or more loosely wound.[24] If the DNA is twisted in the direction of the helix, this is positive supercoiling, and the bases are held more tightly together. If they are twisted in the opposite direction, this is negative supercoiling, and the bases come apart more easily. In nature, most DNA has slight negative supercoiling that is introduced by enzymes called topoisomerases.[25] These enzymes are also needed to relieve the twisting stresses introduced into DNA strands during processes such as transcription and DNA replication.[26]

Alternate DNA structures



From left to right, the structures of A, B and Z DNA

DNA exists in many possible conformations that include A-DNA, B-DNA, and Z-DNA forms, although, only B-DNA and Z-DNA have been directly observed in functional organisms.[9] The conformation that DNA adopts depends on the hydration level, DNA sequence, the amount and direction of supercoiling, chemical modifications of the bases, the type and concentration of metal ions, as well as the presence of polyamines in solution.[27]

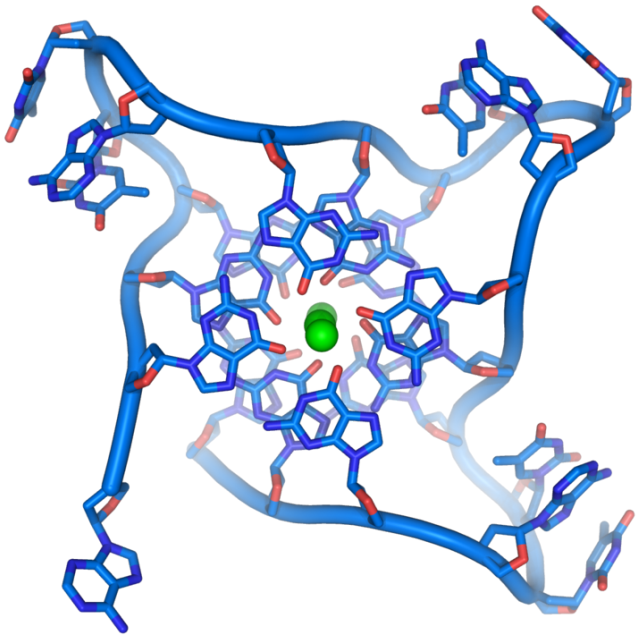
The first published reports of A-DNA X-ray diffraction patterns— and also B-DNA used analyses based on Patterson transforms that provided only a limited amount of structural information for oriented fibers of DNA.[28] [29] An alternate analysis was then proposed by Wilkins *et al.*, in 1953, for the *in vivo* B-DNA X-ray diffraction/scattering patterns of highly

hydrated DNA fibers in terms of squares of Bessel functions.[30] In the same journal, Watson and Crick presented their → molecular modeling analysis of the DNA X-ray diffraction patterns to suggest that the structure was a double-helix.[6]

Although the `B-DNA form' is most common under the conditions found in cells,[31] it is not a well-defined conformation but a family of related DNA conformations[32] that occur at the high hydration levels present in living cells. Their corresponding X-ray diffraction and scattering patterns are characteristic of molecular paracrystals with a significant degree of disorder.[33] [34]

Compared to B-DNA, the A-DNA form is a wider right-handed spiral, with a shallow, wide minor groove and a narrower, deeper major groove. The A form occurs under non-physiological conditions in partially dehydrated samples of DNA, while in the cell it may be produced in hybrid pairings of DNA and RNA strands, as well as in enzyme-DNA complexes.[35] [36] Segments of DNA where the bases have been chemically modified by methylation may undergo a larger change in conformation and adopt the Z form. Here, the strands turn about the helical axis in a left-handed spiral, the opposite of the more common B form.[37] These unusual structures can be recognized by specific Z-DNA binding proteins and may be involved in the regulation of transcription.[38]

Quadruplex structures



Structure of a DNA quadruplex formed by telomere repeats. The looped conformation of the DNA backbone is very different from the typical helical structure.[39]

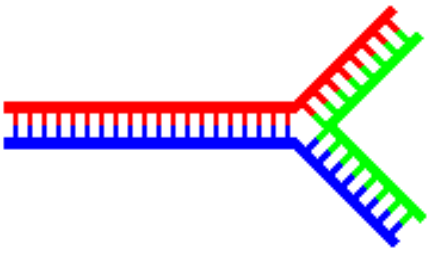
At the ends of the linear chromosomes are specialized regions of DNA called telomeres. The main function of these regions is to allow the cell to replicate chromosome ends using the enzyme telomerase, as the enzymes that normally replicate DNA cannot copy the extreme 3′ ends of chromosomes.[40] These specialized chromosome caps also help protect the DNA ends, and stop the DNA repair systems in the cell from treating them as damage to be corrected.[41] In human cells, telomeres are usually lengths of single-stranded DNA containing several thousand repeats of a simple TTAGGG sequence.[42]

These guanine-rich sequences may stabilize chromosome ends by forming structures of stacked sets of four-base units, rather than the usual base pairs found in other DNA molecules. Here, four guanine bases form a flat plate and these flat four-base units then stack on top of each other, to form a stable *G-quadruplex* structure.[43] These structures are stabilized by hydrogen bonding between the edges of the bases and chelation of a metal ion in the centre of each four-base unit.[44]

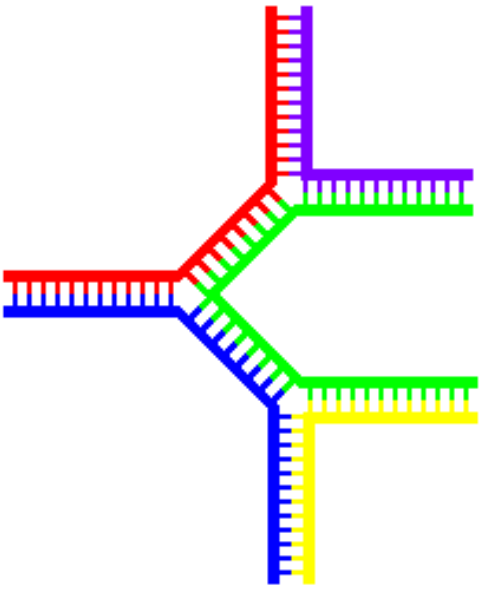
Other structures can also be formed, with the central set of four bases coming from either a single strand folded around the bases, or several different parallel strands, each contributing one base to the central structure.

In addition to these stacked structures, telomeres also form large loop structures called telomere loops, or T-loops. Here, the single-stranded DNA curls around in a long circle stabilized by telomere-binding proteins.[45] At the very end of the T-loop, the single-stranded telomere DNA is held onto a region of double-stranded DNA by the telomere strand disrupting the double-helical DNA and base pairing to one of the two strands. This triple-stranded structure is called a displacement loop or D-loop.[43]

Branched DNA



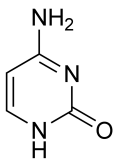
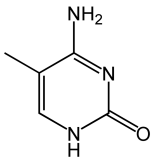
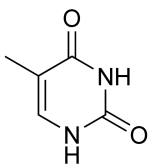
A DNA structure with a single branching point.



A DNA structure with multiple branches.

In DNA fraying occurs when non-complementary regions exist at the end of an otherwise complementary double-strand of DNA. However, branched DNA can occur if a third strand of DNA is introduced and contains adjoining regions able to hybridize with the frayed regions of the pre-existing double-strand. Although the simplest example of branched DNA involves only three strands of DNA, complexes involving additional strands and multiple branches are also possible.[46]

Chemical modifications

		
cytosine	5-methylcytosine	thymine

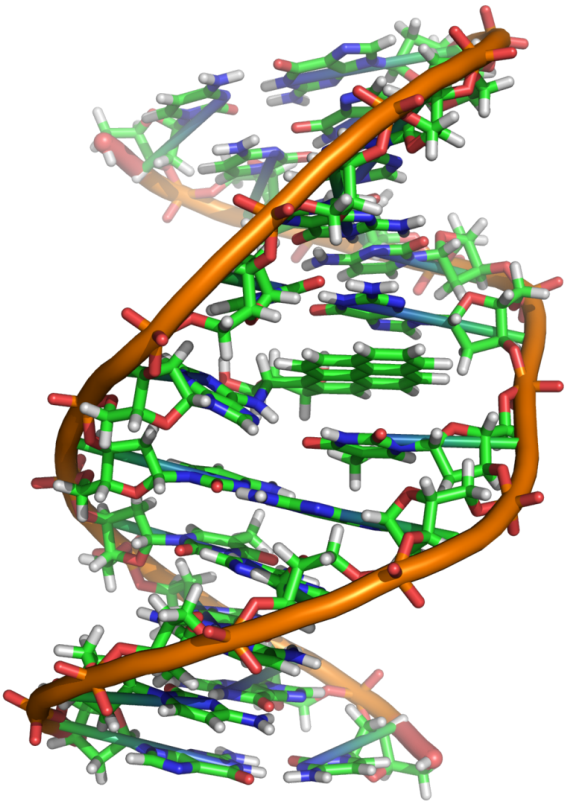
Structure of cytosine with and without the 5-methyl group. After deamination the 5-methylcytosine has the same structure as thymine

Base modifications

The expression of genes is influenced by how the DNA is packaged in chromosomes, in a structure called chromatin. Base modifications can be involved in packaging, with regions that have low or no gene expression usually containing high levels of methylation of cytosine bases. For example, cytosine methylation, produces 5-methylcytosine, which is important for X-chromosome inactivation.[47] The average level of methylation varies between organisms - the worm *Caenorhabditis elegans* lacks cytosine methylation, while vertebrates have higher levels, with up to 1% of their DNA containing 5-methylcytosine.[48] Despite the importance of 5-methylcytosine, it can deaminate to leave a thymine base, methylated cytosines are therefore particularly prone to mutations.[49] Other base modifications include adenine methylation in bacteria, the presence of 5-hydroxymethylcytosine in the brain,[50] and the glycosylation of uracil to produce the "J-base" in kinetoplastids.[51] [52]

Damage

DNA can be damaged by many different sorts of mutagens, which change the DNA sequence. Mutagens include oxidizing agents, alkylating agents and also high-energy electromagnetic radiation such as ultraviolet light and X-rays. The type of DNA damage produced depends on the type of mutagen. For example, UV light can damage DNA by producing thymine dimers, which are cross-links between pyrimidine bases.[54] On the other hand, oxidants such as free radicals or hydrogen peroxide produce multiple forms of damage, including base modifications, particularly of guanosine, and double-strand breaks.[55] A typical human cell contains about 150,000 bases that have suffered oxidative damage.[56] Of these oxidative lesions, the most dangerous are double-strand breaks, as these are difficult to repair and can produce point mutations, insertions and deletions from the DNA sequence, as well as chromosomal translocations.[57]



A covalent adduct between benzo[*a*]pyrene, the major mutagen in tobacco smoke, and DNA[53]

Many mutagens fit into the space between two adjacent base pairs, this is called *intercalating*. Most intercalators are aromatic and planar molecules, and include Ethidium bromide, daunomycin, and doxorubicin. In order for an intercalator to fit between base

pairs, the bases must separate, distorting the DNA strands by unwinding of the double helix. This inhibits both transcription and DNA replication, causing toxicity and mutations. As a result, DNA intercalators are often carcinogens, and Benzo[*a*]pyrene diol epoxide, acridines, aflatoxin and ethidium bromide are well-known examples.[58] [59] [60] Nevertheless, due to their ability to inhibit DNA transcription and replication, other similar toxins are also used in chemotherapy to inhibit rapidly growing cancer cells.[61]

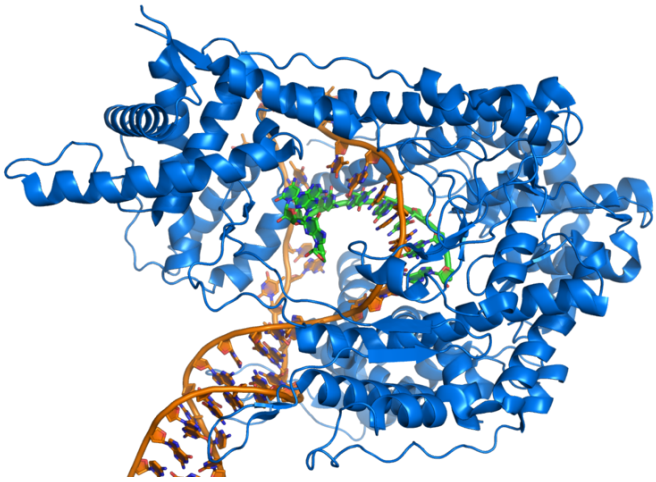
Biological functions

DNA usually occurs as linear chromosomes in eukaryotes, and circular chromosomes in prokaryotes. The set of chromosomes in a cell makes up its genome; the human genome has approximately 3 billion base pairs of DNA arranged into 46 chromosomes.[62] The information carried by DNA is held in the sequence of pieces of DNA called genes. Transmission of genetic information in genes is achieved via complementary base pairing. For example, in transcription, when a cell uses the information in a gene, the DNA sequence is copied into a complementary RNA sequence through the attraction between the DNA and the correct RNA nucleotides. Usually, this RNA copy is then used to make a matching protein sequence in a process called translation which depends on the same interaction between RNA nucleotides. Alternatively, a cell may simply copy its genetic information in a process called DNA replication. The details of these functions are covered in other articles; here we focus on the interactions between DNA and other molecules that mediate the function of the genome.

Genes and genomes

Genomic DNA is located in the cell nucleus of eukaryotes, as well as small amounts in mitochondria and chloroplasts. In prokaryotes, the DNA is held within an irregularly shaped body in the cytoplasm called the nucleoid.[63] The genetic information in a genome is held within genes, and the complete set of this information in an organism is called its genotype. A gene is a unit of heredity and is a region of DNA that influences a particular characteristic in an organism. Genes contain an open reading frame that can be transcribed, as well as regulatory sequences such as promoters and enhancers, which control the transcription of the open reading frame.

In many species, only a small fraction of the total sequence of the genome encodes protein. For example, only about 1.5% of the human genome consists of protein-coding exons, with over 50% of human DNA consisting of non-coding repetitive sequences.[64] The reasons for the presence of so much non-coding DNA in eukaryotic genomes and the extraordinary differences in genome size, or *C-value*, among species represent a long-standing puzzle known as the "C-value enigma."[65] However, DNA sequences that do not code protein may still encode functional non-coding RNA molecules, which are involved in the regulation of gene expression.[66]



T7 RNA polymerase (blue) producing a mRNA (green) from a DNA template (orange).[67]

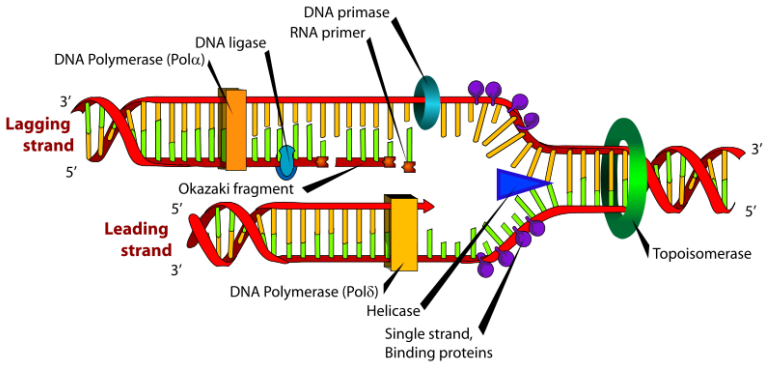
Some non-coding DNA sequences play structural roles in chromosomes. Telomeres and centromeres typically contain few genes, but are important for the function and stability of chromosomes.[41] [68] An abundant form of non-coding DNA in humans are pseudogenes, which are copies of genes that have been disabled by mutation.[69] These sequences are usually just molecular fossils, although they can occasionally serve as raw genetic material for the creation of new genes through the process of gene duplication and divergence.[70]

Transcription and translation

A gene is a sequence of DNA that contains genetic information and can influence the phenotype of an organism. Within a gene, the sequence of bases along a DNA strand defines a messenger RNA sequence, which then defines one or more protein sequences. The relationship between the nucleotide sequences of genes and the amino-acid sequences of proteins is determined by the rules of translation, known collectively as the genetic code. The genetic code consists of three-letter 'words' called *codons* formed from a sequence of three nucleotides (e.g. ACT, CAG, TTT).

In transcription, the codons of a gene are copied into messenger RNA by RNA polymerase. This RNA copy is then decoded by a ribosome that reads the RNA sequence by base-pairing the messenger RNA to transfer RNA, which carries amino acids. Since there are 4 bases in 3-letter combinations, there are 64 possible codons (4^3 combinations). These encode the twenty standard amino acids, giving most amino acids more than one possible codon. There are also three 'stop' or 'nonsense' codons signifying the end of the coding region; these are the TAA, TGA and TAG codons.

Replication



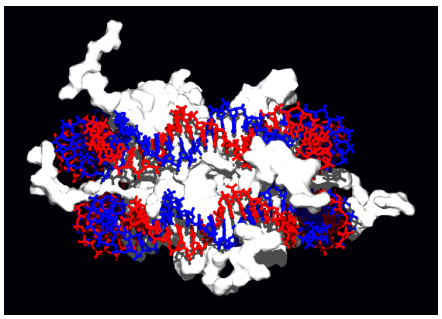
DNA replication. The double helix is unwound by a helicase and topoisomerase. Next, one DNA polymerase produces the leading strand copy. Another DNA polymerase binds to the lagging strand. This enzyme makes discontinuous segments (called Okazaki fragments) before DNA ligase joins them together.

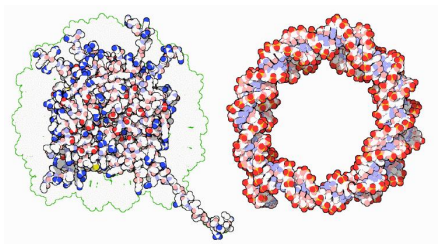
Cell division is essential for an organism to grow, but when a cell divides it must replicate the DNA in its genome so that the two daughter cells have the same genetic information as their parent. The double-stranded structure of DNA provides a simple mechanism for DNA replication. Here, the two strands are separated and then each strand's complementary DNA sequence is recreated by an enzyme called DNA polymerase. This enzyme makes the complementary strand by finding the correct base through complementary base pairing, and bonding it onto the original strand. As DNA polymerases can only extend a DNA strand in a 5′ to 3′ direction, different mechanisms are used to copy the antiparallel strands of the double helix.[71] In this way, the base on the old strand dictates which base appears on the new strand, and the cell ends up with a perfect copy of its DNA.

Interactions with proteins

All the functions of DNA depend on interactions with proteins. These protein interactions can be non-specific, or the protein can bind specifically to a single DNA sequence. Enzymes can also bind to DNA and of these, the polymerases that copy the DNA base sequence in transcription and DNA replication are particularly important.

DNA-binding proteins



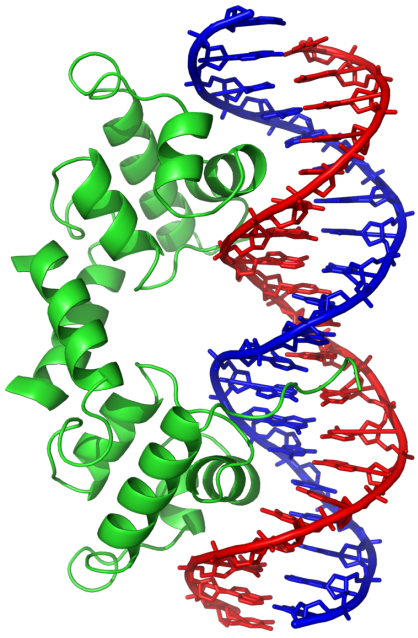


Interaction of DNA with histones (shown in white, top). These proteins' basic amino acids (below left, blue) bind to the acidic phosphate groups on DNA (below right, red).

Structural proteins that bind DNA are well-understood examples of non-specific DNA-protein interactions. Within chromosomes, DNA is held in complexes with structural proteins. These proteins organize the DNA into a compact structure called chromatin. In eukaryotes this structure involves DNA binding to a complex of small basic proteins called histones, while in prokaryotes multiple types of proteins are involved.[72] [73] The histones form a disk-shaped complex called a nucleosome, which contains two complete turns of double-stranded DNA wrapped around its surface. These non-specific interactions are formed through basic residues in the histones making ionic bonds to the acidic sugar-phosphate backbone of the DNA, and are therefore largely independent of the base sequence.[74] Chemical modifications of these basic amino acid residues include methylation, phosphorylation and acetylation.[75] These chemical changes alter the strength of the interaction between the DNA and the histones, making the DNA more or less accessible to transcription factors and changing the rate of transcription.[76] Other non-specific DNA-binding proteins in chromatin include the high-mobility group proteins, which bind to bent or distorted DNA.[77] These proteins are important in bending arrays of nucleosomes and arranging them into the larger structures that make up chromosomes.[78]

A distinct group of DNA-binding proteins are the DNA-binding proteins that specifically bind single-stranded DNA. In humans, replication protein A is the best-understood member of this family and is used in processes where the double helix is separated, including DNA replication, recombination and DNA repair.[79] These binding proteins seem to stabilize single-stranded DNA and protect it from forming stem-loops or being degraded by nucleases.

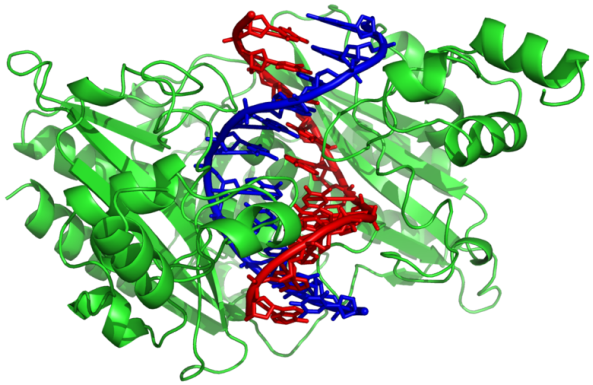
In contrast, other proteins have evolved to bind to particular DNA sequences. The most intensively studied of these are the various transcription factors, which are proteins that regulate transcription. Each transcription factor binds to one particular set of DNA sequences and activates or inhibits the transcription of genes that have these sequences close to their promoters. The transcription factors do this in two ways. Firstly, they can bind the RNA polymerase responsible for transcription, either directly or through other mediator proteins; this locates the polymerase at the promoter and allows it to begin transcription.[81] Alternatively, transcription factors can bind enzymes that modify the histones at the promoter; this will change the accessibility of the DNA template to the polymerase.[82]



The lambda repressor helix-turn-helix transcription factor bound to its DNA target[80]

As these DNA targets can occur throughout an organism's genome, changes in the activity of one type of transcription factor can affect thousands of genes.[83] Consequently, these proteins are often the targets of the signal transduction processes that control responses to environmental changes or cellular differentiation and development. The specificity of these transcription

factors' interactions with DNA come from the proteins making multiple contacts to the edges of the DNA bases, allowing them to "read" the DNA sequence. Most of these base-interactions are made in the major groove, where the bases are most accessible.[84]



The restriction enzyme EcoRV (green) in a complex with its substrate DNA[85]

DNA-modifying enzymes

Nucleases and ligases

Nucleases are enzymes that cut DNA strands by catalyzing the hydrolysis of the phosphodiester bonds. Nucleases that hydrolyse nucleotides from the ends of DNA strands are called exonucleases, while endonucleases cut within strands. The most frequently used nucleases in molecular biology are the restriction endonucleases, which cut DNA at specific sequences. For instance, the EcoRV enzyme shown to the left recognizes the 6-base sequence 5′-GAT|ATC-3′ and makes a cut at the vertical line. In nature, these enzymes protect bacteria against phage infection by digesting the phage DNA when it enters the bacterial cell, acting as part of the restriction modification system.[86] In technology, these sequence-specific nucleases are used in molecular cloning and DNA fingerprinting.

Enzymes called DNA ligases can rejoin cut or broken DNA strands.[87] Ligases are particularly important in lagging strand DNA replication, as they join together the short segments of DNA produced at the replication fork into a complete copy of the DNA template. They are also used in DNA repair and genetic recombination.[87]

Topoisomerases and helicases

Topoisomerases are enzymes with both nuclease and ligase activity. These proteins change the amount of supercoiling in DNA. Some of these enzyme work by cutting the DNA helix and allowing one section to rotate, thereby reducing its level of supercoiling; the enzyme then seals the DNA break.[25] Other types of these enzymes are capable of cutting one DNA helix and then passing a second strand of DNA through this break, before rejoining the helix.[88] Topoisomerases are required for many processes involving DNA, such as DNA replication and transcription.[26]

Helicases are proteins that are a type of molecular motor. They use the chemical energy in nucleoside triphosphates, predominantly ATP, to break hydrogen bonds between bases and unwind the DNA double helix into single strands.[89] These enzymes are essential for most processes where enzymes need to access the DNA bases.

Polymerases

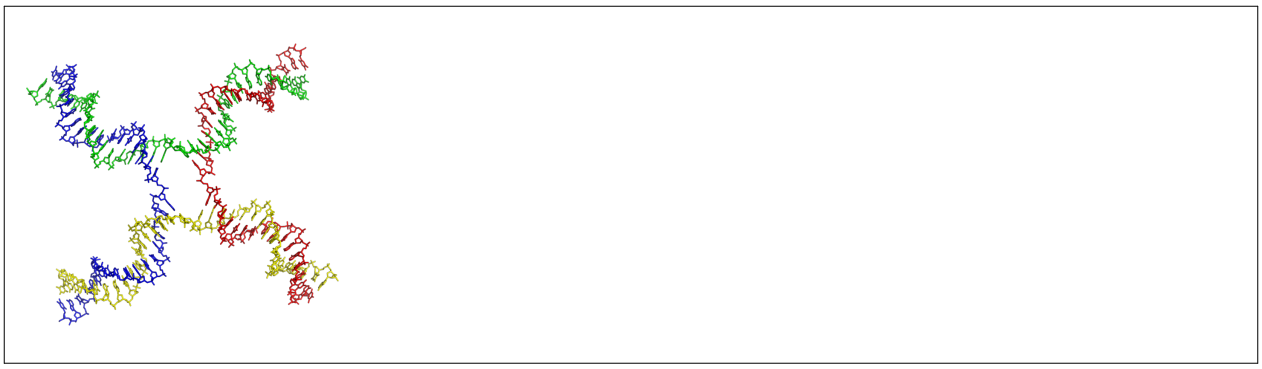
Polymerases are enzymes that synthesize polynucleotide chains from nucleoside triphosphates. The sequence of their products are copies of existing polynucleotide chains - which are called *templates*. These enzymes function by adding nucleotides onto the 3′ hydroxyl group of the previous nucleotide in a DNA strand. Consequently, all polymerases work in a 5′ to 3′ direction.[90] In the active site of these enzymes, the incoming nucleoside triphosphate base-pairs to the template: this allows polymerases to accurately synthesize the complementary strand of their template. Polymerases are classified according to the type of template that they use.

In DNA replication, a DNA-dependent DNA polymerase makes a copy of a DNA sequence. Accuracy is vital in this process, so many of these polymerases have a proofreading activity. Here, the polymerase recognizes the occasional mistakes in the synthesis reaction by the lack of base pairing between the mismatched nucleotides. If a mismatch is detected, a 3′ to 5′ exonuclease activity is activated and the incorrect base removed.[91] In most organisms DNA polymerases function in a large complex called the replisome that contains multiple accessory subunits, such as the DNA clamp or helicases.[92]

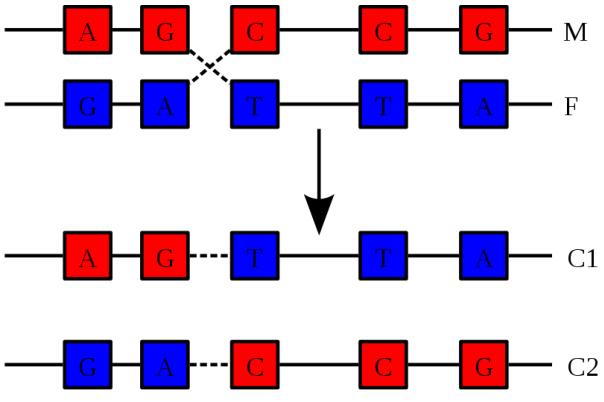
RNA-dependent DNA polymerases are a specialized class of polymerases that copy the sequence of an RNA strand into DNA. They include reverse transcriptase, which is a viral enzyme involved in the infection of cells by retroviruses, and telomerase, which is required for the replication of telomeres.[40] [93] Telomerase is an unusual polymerase because it contains its own RNA template as part of its structure.[41]

Transcription is carried out by a DNA-dependent RNA polymerase that copies the sequence of a DNA strand into RNA. To begin transcribing a gene, the RNA polymerase binds to a sequence of DNA called a promoter and separates the DNA strands. It then copies the gene sequence into a messenger RNA transcript until it reaches a region of DNA called the terminator, where it halts and detaches from the DNA. As with human DNA-dependent DNA polymerases, RNA polymerase II, the enzyme that transcribes most of the genes in the human genome, operates as part of a large protein complex with multiple regulatory and accessory subunits.[94]

Genetic recombination



Structure of the Holliday junction intermediate in genetic recombination. The four separate DNA strands are coloured red, blue, green and yellow.[95]



Recombination involves the breakage and rejoining of two chromosomes (M and F) to produce two re-arranged chromosomes (C1 and C2).

A DNA helix usually does not interact with other segments of DNA, and in human cells the different chromosomes even occupy separate areas in the nucleus called "chromosome territories".[96] This physical separation of different chromosomes is important for the ability of DNA to function as a stable repository for information, as one of the few times chromosomes interact is during chromosomal crossover when they recombine. Chromosomal crossover is when two DNA helices break, swap a section and then rejoin.

Recombination allows chromosomes to exchange genetic information and produces new combinations of genes, which increases the efficiency of natural selection and can be important in the rapid evolution of new proteins.[97] Genetic recombination can also be involved in DNA repair, particularly in the cell's response to double-strand breaks.[98]

The most common form of chromosomal crossover is homologous recombination, where the two chromosomes involved share very similar sequences. Non-homologous recombination can be damaging to cells, as it can produce chromosomal translocations and genetic abnormalities. The recombination reaction is catalyzed by enzymes known as *recombinases*, such as RAD51.[99] The first step in recombination is a double-stranded break either caused by an endonuclease or damage to the DNA.[100] A series of steps catalyzed in part by the recombinase then leads to joining of the two helices by at least one Holliday junction, in which a segment of a single strand in each helix is annealed to the complementary strand in the other helix. The Holliday junction is a tetrahedral junction structure that can be moved along the pair of chromosomes, swapping one strand for another. The recombination reaction is then halted by cleavage of the junction and re-ligation of the released DNA.[101]

Evolution

DNA contains the genetic information that allows all modern living things to function, grow and reproduce. However, it is unclear how long in the 4-billion-year history of life DNA has performed this function, as it has been proposed that the earliest forms of life may have used RNA as their genetic material.[90] [102] RNA may have acted as the central part of early cell metabolism as it can both transmit genetic information and carry out catalysis as part of ribozymes.[103] This ancient RNA world where nucleic acid would have been used for both catalysis and genetics may have influenced the evolution of the current genetic code based on four nucleotide bases. This would occur since the number of unique bases in such an organism is a trade-off between a small number of bases increasing replication accuracy and a large number of bases increasing the catalytic efficiency of ribozymes.[104]

Unfortunately, there is no direct evidence of ancient genetic systems, as recovery of DNA from most fossils is impossible. This is because DNA will survive in the environment for less than one million years and slowly degrades into short fragments in solution.[105] Claims for older DNA have been made, most notably a report of the isolation of a viable bacterium from a salt crystal 250-million years old,[106] but these claims are controversial.[107] [108]

Uses in technology

Genetic engineering

Methods have been developed to purify DNA from organisms, such as phenol-chloroform extraction and manipulate it in the laboratory, such as restriction digests and the → polymerase chain reaction. Modern biology and biochemistry make intensive use of these techniques in recombinant DNA technology. Recombinant DNA is a man-made DNA sequence that has been assembled from other DNA sequences. They can be transformed into organisms in the form of plasmids or in the appropriate format, by using a viral vector.[109] The genetically modified organisms produced can be used to produce products such as recombinant proteins, used in medical research,[110] or be grown in agriculture.[111] [112]

Forensics

Forensic scientists can use DNA in blood, semen, skin, saliva or hair found at a crime scene to identify a matching DNA of an individual, such as a perpetrator. This process is called genetic fingerprinting, or more accurately, DNA profiling. In DNA profiling, the lengths of variable sections of repetitive DNA, such as short tandem repeats and minisatellites, are compared between people. This method is usually an extremely reliable technique for identifying a matching DNA.[113] However, identification can be complicated if the scene is contaminated with DNA from several people.[114] DNA profiling was developed in 1984 by British geneticist Sir Alec Jeffreys,[115] and first used in forensic science to convict Colin Pitchfork in the 1988 Enderby murders case.[116]

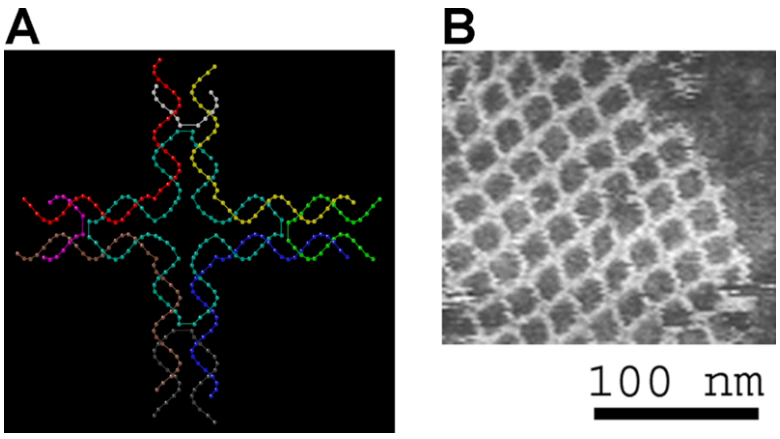
People convicted of certain types of crimes may be required to provide a sample of DNA for a database. This has helped investigators solve old cases where only a DNA sample was obtained from the scene. DNA profiling can also be used to identify victims of mass casualty incidents.[117] On the other hand, many convicted people have been released from prison on the basis of DNA techniques, which were not available when a crime had originally been committed.

Bioinformatics

Bioinformatics involves the manipulation, searching, and data mining of DNA sequence data. The development of techniques to store and search DNA sequences have led to widely applied advances in computer science, especially string searching algorithms, machine learning and database theory.[118] String searching or matching algorithms, which find an occurrence of a sequence of letters inside a larger sequence of letters, were developed to search for specific sequences of nucleotides.[119] In other applications such as text editors, even simple algorithms for this problem usually suffice, but DNA sequences cause these algorithms to exhibit near-worst-case behaviour due to their small number of distinct characters. The related problem of sequence alignment aims to identify homologous sequences and locate the specific mutations that make them distinct. These techniques, especially multiple sequence alignment, are used in studying phylogenetic relationships and protein function.[120] Data sets representing entire genomes' worth of DNA sequences, such as those produced by the Human Genome Project, are difficult to use without annotations, which label the locations of genes and regulatory elements on each chromosome. Regions of DNA sequence that have the characteristic patterns associated with protein- or RNA-coding genes can be identified by gene finding algorithms, which allow researchers to predict the presence of particular gene products in an organism even before they have been isolated experimentally.[121]

DNA nanotechnology

DNA nanotechnology uses the unique molecular recognition properties of DNA and other nucleic acids to create self-assembling branched DNA complexes with useful properties.[123] DNA is thus used as a structural material rather than as a carrier of biological information. This has led to the creation of two-dimensional periodic lattices (both tile-based as well as using the "DNA origami" method) as well as three-dimensional structures in the shapes of polyhedra.[124] Nanomechanical devices and algorithmic self-assembly have also been demonstrated,[125] and these DNA structures have been used to template the arrangement of other molecules such as gold nanoparticles and streptavidin proteins.[126]



The DNA structure at left (schematic shown) will self-assemble into the structure visualized by atomic force microscopy at right. → DNA nanotechnology is the field which seeks to design nanoscale structures using the molecular recognition properties of DNA molecules. Image from Strong, 2004.[122]

History and anthropology

Because DNA collects mutations over time, which are then inherited, it contains historical information and by comparing DNA sequences, geneticists can infer the evolutionary history of organisms, their phylogeny.[127] This field of phylogenetics is a powerful tool in

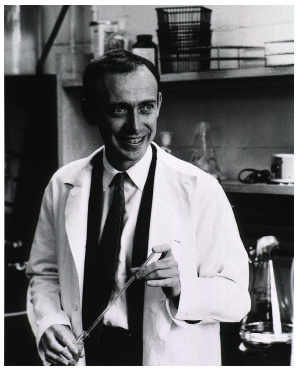
evolutionary biology. If DNA sequences within a species are compared, population geneticists can learn the history of particular populations. This can be used in studies ranging from ecological genetics to anthropology; for example, DNA evidence is being used to try to identify the Ten Lost Tribes of Israel.[128] [129]

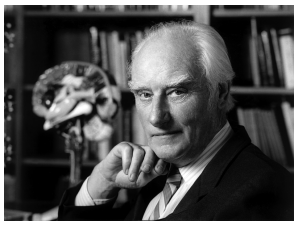
DNA has also been used to look at modern family relationships, such as establishing family relationships between the descendants of Sally Hemings and Thomas Jefferson. This usage is closely related to the use of DNA in criminal investigations detailed above. Indeed, some criminal investigations have been solved when DNA from crime scenes has matched relatives of the guilty individual.[130]

History of DNA research

DNA was first isolated by the Swiss physician Friedrich Miescher who, in 1869, discovered a microscopic substance in the pus of discarded surgical bandages. As it resided in the nuclei of cells, he called it "nuclein".[131] In 1919, Phoebus Levene identified the base, sugar and phosphate nucleotide unit.[132] Levene suggested that DNA consisted of a string of nucleotide units linked together through the phosphate groups. However, Levene thought the chain was short and the bases repeated in a fixed order. In 1937 William Astbury produced the first X-ray diffraction patterns that showed that DNA had a regular structure.[133]

In 1928, Frederick Griffith discovered that traits of the "smooth" form of the *Pneumococcus* could be transferred to the "rough" form of the same bacteria by mixing killed "smooth" bacteria with the live "rough" form.[134] This system provided the first clear suggestion that DNA carried genetic information—the Avery-MacLeod-McCarty experiment—when Oswald Avery, along with coworkers Colin MacLeod and Maclyn McCarty, identified DNA as the transforming principle in 1943.[135] DNA's role in heredity was confirmed in 1952, when Alfred Hershey and Martha Chase in the Hershey-Chase experiment showed that DNA is the genetic material of the T2 phage.[136]


James D. Watson

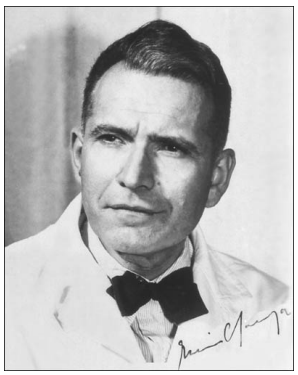

Francis Crick


Francis Crick

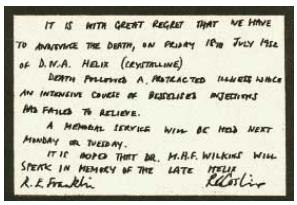

Rosalind Franklin

Raymond Gosling

Maurice F.Wilkins



Erwin Chargaff



DNA Helix controversy

In 1953 James D. Watson and Francis Crick suggested what is now accepted as the first correct double-helix model of DNA structure in the journal *Nature*.[6] Their double-helix, molecular model of DNA was then based on a single X-ray diffraction image (labeled as "Photo 51")[137] taken by Rosalind Franklin and Raymond Gosling in May 1952, as well as the information that the DNA bases were paired—also obtained through private communications from Erwin Chargaff in the previous years. Chargaff's rules played a very important role in establishing double-helix configurations for B-DNA as well as A-DNA.

Experimental evidence supporting the Watson and Crick model were published in a series of five articles in the same issue of *Nature*.[138] Of these, Franklin and Gosling's paper was the first publication of their own X-ray diffraction data and original analysis method that partially supported the Watson and Crick model[29] [139] ; this issue also contained an article on DNA structure by Maurice Wilkins and two of his colleagues, whose analysis and *in vivo* B-DNA X-ray patterns also supported the presence *in vivo* of the double-helical DNA configurations as proposed by Crick and Watson for their double-helix molecular model of DNA in the previous two pages of *Nature*.[30] In 1962, after Franklin's death, Watson, Crick, and Wilkins jointly received the Nobel Prize in Physiology or Medicine.[140] Unfortunately, Nobel rules of the time allowed only living recipients, but a vigorous debate continues on who should receive credit for the discovery.[141]

In an influential presentation in 1957, Crick laid out the "Central Dogma" of molecular biology, which foretold the relationship between DNA, RNA, and proteins, and articulated the "adaptor hypothesis".[142] Final confirmation of the replication mechanism that was implied by the double-helical structure followed in 1958 through the Meselson-Stahl experiment.[143] Further work by Crick and coworkers showed that the genetic code was based on non-overlapping triplets of bases, called codons, allowing Har Gobind Khorana, Robert W. Holley and Marshall Warren Nirenberg to decipher the genetic code.[144] These findings represent the birth of molecular biology.

See also

- Molecular Structure of Nucleic Acids: A Structure for Deoxyribose Nucleic Acid
- → Molecular models of DNA
- → DNA microarray
- DNA sequencing
- Paracrystal model and theory
- X-ray scattering
- Crystallography
- X-ray crystallography
- Genetic disorder
- Junk DNA
- Nucleic acid analogues
- Nucleic acid methods
- Nucleic acid modeling
- Nucleic Acid Notations
- Phosphoramidite
- Plasmid
- → Polymerase chain reaction
- *Proteopedia DNA* [145]
- Southern blot
- Triple-stranded DNA

Notes

[1] Saenger, Wolfram (1984). *Principles of Nucleic Acid Structure*. New York: Springer-Verlag. ISBN 0387907629.

[2] Alberts, Bruce; Alexander Johnson, Julian Lewis, Martin Raff, Keith Roberts, and Peter Walters (2002). *Molecular Biology of the Cell; Fourth Edition (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowTOC&rid=mboc4.TOC&depth=2)*. New York and London: Garland Science. ISBN 0-8153-3218-1. OCLC 145080076 48122761 57023651 69932405 (http://worldcat.org/oclc/145080076+48122761+57023651+69932405). .

[3] Butler, John M. (2001). *Forensic DNA Typing*. Elsevier. ISBN 978-0-12-147951-0. OCLC 223032110 45406517 (http://worldcat.org/oclc/223032110+45406517). pp. 14–15.

[4] Mandelkern M, Elias J, Eden D, Crothers D (1981). "The dimensions of DNA in solution". *J Mol Biol* **152** (1): 153–61. doi: 10.1016/0022-2836(81)90099-1 (http://dx.doi.org/10.1016/0022-2836(81)90099-1). PMID 7338906.

[5] Gregory S, *et al.* (2006). "The DNA sequence and biological annotation of human chromosome 1". *Nature* **441** (7091): 315–21. doi: 10.1038/nature04727 (http://dx.doi.org/10.1038/nature04727). PMID 16710414.

[6] Watson J.D. and Crick F.H.C. (1953). " A Structure for Deoxyribose Nucleic Acid (http://www.nature.com/nature/dna50/watsoncrick.pdf)" (PDF). *Nature* **171**: 737–738. doi: 10.1038/171737a0 (http://dx.doi.org/10.1038/171737a0). PMID 13054692. . Retrieved on 4 May 2009.

[7] Berg J., Tymoczko J. and Stryer L. (2002) *Biochemistry.* W. H. Freeman and Company ISBN 0-7167-4955-6

[8] Abbreviations and Symbols for Nucleic Acids, Polynucleotides and their Constituents (http://www.chem.qmul.ac.uk/iupac/misc/naabb.html) IUPAC-IUB Commission on Biochemical Nomenclature (CBN), Accessed 03 January 2006

[9] Ghosh A, Bansal M (2003). "A glossary of DNA structures from A to Z". *Acta Crystallogr D Biol Crystallogr* **59** (Pt 4): 620–6. doi: 10.1107/S0907444903003251 (http://dx.doi.org/10.1107/S0907444903003251). PMID 12657780.

[10] Created from PDB 1D65 (http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=1D65)

[11] Wing R, Drew H, Takano T, Broka C, Tanaka S, Itakura K, Dickerson R (1980). "Crystal structure analysis of a complete turn of B-DNA". *Nature* **287** (5784): 755–8. doi: 10.1038/287755a0 (http://dx.doi.org/10.1038/287755a0). PMID 7432492.

[12] Pabo C, Sauer R (1984). "Protein-DNA recognition". *Annu Rev Biochem* **53**: 293–321. doi: 10.1146/annurev.bi.53.070184.001453 (http://dx.doi.org/10.1146/annurev.bi.53.070184.001453). PMID

6236744.

[13] Clausen-Schaumann H, Rief M, Tolksdorf C, Gaub H (2000). " Mechanical stability of single DNA molecules (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=1300792)". *Biophys J* **78** (4): 1997–2007. doi: 10.1016/S0006-3495(00)76747-6 (http://dx.doi.org/10.1016/S0006-3495(00)76747-6). PMID 10733978.

[14] Yakovchuk P, Protozanova E, Frank-Kamenetskii MD (2006). " Base-stacking and base-pairing contributions into thermal stability of the DNA double helix (http://nar.oxfordjournals.org/cgi/pmidlookup?view=long&pmid=16449200)". *Nucleic Acids Res.* **34** (2): 564–74. doi: 10.1093/nar/gkj454 (http://dx.doi.org/10.1093/nar/gkj454). PMID 16449200. PMC: 1360284 (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=1360284). .

[15] Chalikian T, Völker J, Plum G, Breslauer K (1999). " A more unified picture for the thermodynamics of nucleic acid duplex melting: a characterization by calorimetric and volumetric techniques (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=22151)". *Proc Natl Acad Sci USA* **96** (14): 7853–8. doi: 10.1073/pnas.96.14.7853 (http://dx.doi.org/10.1073/pnas.96.14.7853). PMID 10393911.

[16] deHaseth P, Helmann J (1995). "Open complex formation by Escherichia coli RNA polymerase: the mechanism of polymerase-induced strand separation of double helical DNA". *Mol Microbiol* **16** (5): 817–24. doi: 10.1111/j.1365-2958.1995.tb02309.x (http://dx.doi.org/10.1111/j.1365-2958.1995.tb02309.x). PMID 7476180.

[17] Isaksson J, Acharya S, Barman J, Cheruku P, Chattopadhyaya J (2004). "Single-stranded adenine-rich DNA and RNA retain structural characteristics of their respective double-stranded conformations and show directional differences in stacking pattern". *Biochemistry* **43** (51): 15996–6010. doi: 10.1021/bi048221v (http://dx.doi.org/10.1021/bi048221v). PMID 15609994.

[18] Designation of the two strands of DNA (http://www.chem.qmul.ac.uk/iubmb/newsletter/misc/DNA.html) JCBN/NC-IUB Newsletter 1989, Accessed 07 May 2008

[19] Hüttenhofer A, Schattner P, Polacek N (2005). "Non-coding RNAs: hope or hype?". *Trends Genet* **21** (5): 289–97. doi: 10.1016/j.tig.2005.03.007 (http://dx.doi.org/10.1016/j.tig.2005.03.007). PMID 15851066.

[20] Munroe S (2004). "Diversity of antisense regulation in eukaryotes: multiple mechanisms, emerging patterns". *J Cell Biochem* **93** (4): 664–71. doi: 10.1002/jcb.20252 (http://dx.doi.org/10.1002/jcb.20252). PMID 15389973.

[21] Makalowska I, Lin C, Makalowski W (2005). "Overlapping genes in vertebrate genomes". *Comput Biol Chem* **29** (1): 1–12. doi: 10.1016/j.compbiolchem.2004.12.006 (http://dx.doi.org/10.1016/j.compbiolchem.2004.12.006). PMID 15680581.

[22] Johnson Z, Chisholm S (2004). "Properties of overlapping genes are conserved across microbial genomes". *Genome Res* **14** (11): 2268–72. doi: 10.1101/gr.2433104 (http://dx.doi.org/10.1101/gr.2433104). PMID 15520290.

[23] Lamb R, Horvath C (1991). "Diversity of coding strategies in influenza viruses". *Trends Genet* **7** (8): 261–6. PMID 1771674.

[24] Benham C, Mielke S (2005). "DNA mechanics". *Annu Rev Biomed Eng* **7**: 21–53. doi: 10.1146/annurev.bioeng.6.062403.132016 (http://dx.doi.org/10.1146/annurev.bioeng.6.062403.132016). PMID 16004565.

[25] Champoux J (2001). "DNA topoisomerases: structure, function, and mechanism". *Annu Rev Biochem* **70**: 369–413. doi: 10.1146/annurev.biochem.70.1.369 (http://dx.doi.org/10.1146/annurev.biochem.70.1.369). PMID 11395412.

[26] Wang J (2002). "Cellular roles of DNA topoisomerases: a molecular perspective". *Nat Rev Mol Cell Biol* **3** (6): 430–40. doi: 10.1038/nrm831 (http://dx.doi.org/10.1038/nrm831). PMID 12042765.

[27] Basu H, Feuerstein B, Zarling D, Shafer R, Marton L (1988). "Recognition of Z-RNA and Z-DNA determinants by polyamines in solution: experimental and theoretical studies". *J Biomol Struct Dyn* **6** (2): 299–309. PMID 2482766.

[28] Franklin RE, Gosling RG (6 March 1953). " The Structure of Sodium Thymonucleate Fibres I. The Influence of Water Content (http://hekto.med.unc.edu:8080/CARTER/carter_WWW/Bioch_134/PDF_files/Franklin_Gossling.pdf)". *Acta Cryst* **6** (8-9): 673–7. doi: 10.1107/S0365110X53001939 (http://dx.doi.org/10.1107/S0365110X53001939). .

Franklin RE, Gosling RG (September 1953). "The structure of sodium thymonucleate fibres. II. The cylindrically symmetrical Patterson function". *Acta Cryst* **6** (8-9): 678–85. doi: 10.1107/S0365110X53001940 (http://dx.doi.org/10.1107/S0365110X53001940).

[29] Franklin, Rosalind and Gosling, Raymond (1953). " Molecular Configuration in Sodium Thymonucleate. Franklin R. and Gosling R.G (http://www.nature.com/nature/dna50/franklingosling.pdf)" (PDF). *Nature* **171**: 740–1. doi: 10.1038/171740a0 (http://dx.doi.org/10.1038/171740a0). PMID 13054694. .

[30] Wilkins M.H.F., A.R. Stokes A.R. & Wilson, H.R. (1953). " Molecular Structure of Deoxypentose Nucleic Acids (http://www.nature.com/nature/dna50/wilkins.pdf)" (PDF). *Nature* **171**: 738–740. doi: 10.1038/171738a0 (http://dx.doi.org/10.1038/171738a0). PMID 13054693. .

[31] Leslie AG, Arnott S, Chandrasekaran R, Ratliff RL (1980). "Polymorphism of DNA double helices". *J. Mol. Biol.* **143** (1): 49–72. doi: 10.1016/0022-2836(80)90124-2 (http://dx.doi.org/10.1016/0022-2836(80)90124-2). PMID 7441761.

[32] Baianu, I.C. (1980). "Structural Order and Partial Disorder in Biological systems". *Bull. Math. Biol.* **42** (4): 137–141. http://cogprints.org/3822/

[33] Hosemann R., Bagchi R.N., *Direct analysis of diffraction by matter*, North-Holland Publs., Amsterdam – New York, 1962.

[34] Baianu, I.C. (1978). "X-ray scattering by partially disordered membrane systems.". *Acta Cryst.,* **A34** (5): 751–753. doi: 10.1107/S0567739478001540 (http://dx.doi.org/10.1107/S0567739478001540).

[35] Wahl M, Sundaralingam M (1997). "Crystal structures of A-DNA duplexes". *Biopolymers* **44** (1): 45–63. doi:10.1002/(SICI)1097-0282(1997)44:1 (inactive 2009-03-14) . PMID 9097733.

[36] Lu XJ, Shakked Z, Olson WK (2000). "A-form conformational motifs in ligand-bound DNA structures". *J. Mol. Biol.* **300** (4): 819–40. doi: 10.1006/jmbi.2000.3690 (http://dx.doi.org/10.1006/jmbi.2000.3690). PMID 10891271.

[37] Rothenburg S, Koch-Nolte F, Haag F (2001). "DNA methylation and Z-DNA formation as mediators of quantitative differences in the expression of alleles". *Immunol Rev* **184**: 286–98. doi: 10.1034/j.1600-065x.2001.1840125.x (http://dx.doi.org/10.1034/j.1600-065x.2001.1840125.x). PMID 12086319.

[38] Oh D, Kim Y, Rich A (2002). " Z-DNA-binding proteins can act as potent effectors of gene expression in vivo (http://www.pnas.org/cgi/pmidlookup?view=long&pmid=12486233)". *Proc. Natl. Acad. Sci. U.S.A.* **99** (26): 16666–71. doi: 10.1073/pnas.262672699 (http://dx.doi.org/10.1073/pnas.262672699). PMID 12486233. PMC: 139201 (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=139201). .

[39] Created from NDB UD0017 (http://ndbserver.rutgers.edu/atlas/xray/structures/U/ud0017/ud0017.html)

[40] Greider C, Blackburn E (1985). "Identification of a specific telomere terminal transferase activity in Tetrahymena extracts". *Cell* **43** (2 Pt 1): 405–13. doi: 10.1016/0092-8674(85)90170-9 (http://dx.doi.org/10.1016/0092-8674(85)90170-9). PMID 3907856.

[41] Nugent C, Lundblad V (1998). " The telomerase reverse transcriptase: components and regulation (http://www.genesdev.org/cgi/content/full/12/8/1073)". *Genes Dev* **12** (8): 1073–85. doi: 10.1101/gad.12.8.1073 (http://dx.doi.org/10.1101/gad.12.8.1073). PMID 9553037. .

[42] Wright W, Tesmer V, Huffman K, Levene S, Shay J (1997). " Normal human chromosomes have long G-rich telomeric overhangs at one end (http://www.genesdev.org/cgi/content/full/11/21/2801)". *Genes Dev* **11** (21): 2801–9. doi: 10.1101/gad.11.21.2801 (http://dx.doi.org/10.1101/gad.11.21.2801). PMID 9353250. .

[43] Burge S, Parkinson G, Hazel P, Todd A, Neidle S (2006). " Quadruplex DNA: sequence, topology and structure (http://nar.oxfordjournals.org/cgi/pmidlookup?view=long&pmid=17012276)". *Nucleic Acids Res* **34** (19): 5402–15. doi: 10.1093/nar/gkl655 (http://dx.doi.org/10.1093/nar/gkl655). PMID 17012276. PMC: 1636468 (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=1636468). .

[44] Parkinson G, Lee M, Neidle S (2002). "Crystal structure of parallel quadruplexes from human telomeric DNA". *Nature* **417** (6891): 876–80. doi: 10.1038/nature755 (http://dx.doi.org/10.1038/nature755). PMID 12050675.

[45] Griffith J, Comeau L, Rosenfield S, Stansel R, Bianchi A, Moss H, de Lange T (1999). "Mammalian telomeres end in a large duplex loop". *Cell* **97** (4): 503–14. doi: 10.1016/S0092-8674(00)80760-6 (http://dx.doi.org/10.1016/S0092-8674(00)80760-6). PMID 10338214.

[46] Seeman NC (November 2005). "DNA enables nanoscale control of the structure of matter". *Q. Rev. Biophys.* **38** (4): 363–71. doi: 10.1017/S0033583505004087 (http://dx.doi.org/10.1017/S0033583505004087). PMID 16515737.

[47] Klose R, Bird A (2006). "Genomic DNA methylation: the mark and its mediators". *Trends Biochem Sci* **31** (2): 89–97. doi: 10.1016/j.tibs.2005.12.008 (http://dx.doi.org/10.1016/j.tibs.2005.12.008). PMID 16403636.

[48] Bird A (2002). "DNA methylation patterns and epigenetic memory". *Genes Dev* **16** (1): 6–21. doi: 10.1101/gad.947102 (http://dx.doi.org/10.1101/gad.947102). PMID 11782440.

[49] Walsh C, Xu G (2006). "Cytosine methylation and DNA repair". *Curr Top Microbiol Immunol* **301**: 283–315. doi: 10.1007/3-540-31390-7_11 (http://dx.doi.org/10.1007/3-540-31390-7_11). PMID 16570853.

[50] Kriaucionis S, Heintz N (May 2009). "The nuclear DNA base 5-hydroxymethylcytosine is present in Purkinje neurons and the brain". *Science* **324** (5929): 929–30. doi: 10.1126/science.1169786 (http://dx.doi.org/10.1126/science.1169786). PMID 19372393.

[51] Ratel D, Ravanat J, Berger F, Wion D (2006). "N6-methyladenine: the other methylated base of DNA". *Bioessays* **28** (3): 309–15. doi: 10.1002/bies.20342 (http://dx.doi.org/10.1002/bies.20342). PMID 16479578.

[52] Gommers-Ampt J, Van Leeuwen F, de Beer A, Vliegenthart J, Dizdaroglu M, Kowalak J, Crain P, Borst P (1993). "beta-D-glucosyl-hydroxymethyluracil: a novel modified base present in the DNA of the parasitic protozoan T. brucei". *Cell* **75** (6): 1129–36. doi: 10.1016/0092-8674(93)90322-H (http://dx.doi.org/10.1016/0092-8674(93)90322-H). PMID 8261512.
[53] Created from PDB 1JDG (http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=1JDG)
[54] Douki T, Reynaud-Angelin A, Cadet J, Sage E (2003). "Bipyrimidine photoproducts rather than oxidative lesions are the main type of DNA damage involved in the genotoxic effect of solar UVA radiation". *Biochemistry* **42** (30): 9221–6. doi: 10.1021/bi034593c (http://dx.doi.org/10.1021/bi034593c). PMID 12885257.,
[55] Cadet J, Delatour T, Douki T, Gasparutto D, Pouget J, Ravanat J, Sauvaigo S (1999). "Hydroxyl radicals and DNA base damage". *Mutat Res* **424** (1–2): 9–21. PMID 10064846.
[56] Beckman KB, Ames BN (August 1997). " Oxidative decay of DNA (http://www.jbc.org/cgi/pmidlookup?view=long&pmid=9289489)". *J. Biol. Chem.* **272** (32): 19633–6. PMID 9289489. .
[57] Valerie K, Povirk L (2003). "Regulation and mechanisms of mammalian double-strand break repair". *Oncogene* **22** (37): 5792–812. doi: 10.1038/sj.onc.1206679 (http://dx.doi.org/10.1038/sj.onc.1206679). PMID 12947387.
[58] Ferguson L, Denny W (1991). "The genetic toxicology of acridines". *Mutat Res* **258** (2): 123–60. PMID 1881402.
[59] Jeffrey A (1985). "DNA modification by chemical carcinogens". *Pharmacol Ther* **28** (2): 237–72. doi: 10.1016/0163-7258(85)90013-0 (http://dx.doi.org/10.1016/0163-7258(85)90013-0). PMID 3936066.
[60] Stephens T, Bunde C, Fillmore B (2000). "Mechanism of action in thalidomide teratogenesis". *Biochem Pharmacol* **59** (12): 1489–99. doi: 10.1016/S0006-2952(99)00388-3 (http://dx.doi.org/10.1016/S0006-2952(99)00388-3). PMID 10799645.
[61] Braña M, Cacho M, Gradillas A, de Pascual-Teresa B, Ramos A (2001). "Intercalators as anticancer drugs". *Curr Pharm Des* **7** (17): 1745–80. doi: 10.2174/1381612013397113 (http://dx.doi.org/10.2174/1381612013397113). PMID 11562309.
[62] Venter J, *et al.* (2001). "The sequence of the human genome". *Science* **291** (5507): 1304–51. doi: 10.1126/science.1058040 (http://dx.doi.org/10.1126/science.1058040). PMID 11181995.
[63] Thanbichler M, Wang S, Shapiro L (2005). "The bacterial nucleoid: a highly organized and dynamic structure". *J Cell Biochem* **96** (3): 506–21. doi: 10.1002/jcb.20519 (http://dx.doi.org/10.1002/jcb.20519). PMID 15988757.
[64] Wolfsberg T, McEntyre J, Schuler G (2001). "Guide to the draft human genome". *Nature* **409** (6822): 824–6. doi: 10.1038/35057000 (http://dx.doi.org/10.1038/35057000). PMID 11236998.
[65] Gregory T (2005). " The C-value enigma in plants and animals: a review of parallels and an appeal for partnership (http://aob.oxfordjournals.org/cgi/content/full/95/1/133)". *Ann Bot (Lond)* **95** (1): 133–46. doi: 10.1093/aob/mci009 (http://dx.doi.org/10.1093/aob/mci009). PMID 15596463. .
[66] The ENCODE Project Consortium (2007). "Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project". *Nature* **447** (7146): 799–816. doi: 10.1038/nature05874 (http://dx.doi.org/10.1038/nature05874).
[67] Created from PDB 1MSW (http://www.rcsb.org/pdb/explore/explore.do?structureId=1MSW)
[68] Pidoux A, Allshire R (2005). " The role of heterochromatin in centromere function (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=1569473)". *Philos Trans R Soc Lond B Biol Sci* **360** (1455): 569–79. doi: 10.1098/rstb.2004.1611 (http://dx.doi.org/10.1098/rstb.2004.1611). PMID 15905142.
[69] Harrison P, Hegyi H, Balasubramanian S, Luscombe N, Bertone P, Echols N, Johnson T, Gerstein M (2002). " Molecular fossils in the human genome: identification and analysis of the pseudogenes in chromosomes 21 and 22 (http://www.genome.org/cgi/content/full/12/2/272)". *Genome Res* **12** (2): 272–80. doi: 10.1101/gr.207102 (http://dx.doi.org/10.1101/gr.207102). PMID 11827946. .
[70] Harrison P, Gerstein M (2002). "Studying genomes through the aeons: protein families, pseudogenes and proteome evolution". *J Mol Biol* **318** (5): 1155–74. doi: 10.1016/S0022-2836(02)00109-2 (http://dx.doi.org/10.1016/S0022-2836(02)00109-2). PMID 12083509.
[71] Albà M (2001). " Replicative DNA polymerases (http://genomebiology.com/1465-6906/2/REVIEWS3002)". *Genome Biol* **2** (1): REVIEWS3002. doi: 10.1186/gb-2001-2-1-reviews3002 (http://dx.doi.org/10.1186/gb-2001-2-1-reviews3002). PMID 11178285. PMC: 150442 (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=150442). .
[72] Sandman K, Pereira S, Reeve J (1998). "Diversity of prokaryotic chromosomal proteins and the origin of the nucleosome". *Cell Mol Life Sci* **54** (12): 1350–64. doi: 10.1007/s000180050259 (http://dx.doi.org/10.1007/s000180050259). PMID 9893710.
[73] Dame RT (2005). "The role of nucleoid-associated proteins in the organization and compaction of bacterial chromatin". *Mol. Microbiol.* **56** (4): 858–70. doi: 10.1111/j.1365-2958.2005.04598.x (http://dx.doi.org/10.

1111/j.1365-2958.2005.04598.x). PMID 15853876.
[74] Luger K, Mäder A, Richmond R, Sargent D, Richmond T (1997). "Crystal structure of the nucleosome core particle at 2.8 A resolution". *Nature* **389** (6648): 251–60. doi: 10.1038/38444 (http://dx.doi.org/10.1038/38444). PMID 9305837.
[75] Jenuwein T, Allis C (2001). "Translating the histone code". *Science* **293** (5532): 1074–80. doi: 10.1126/science.1063127 (http://dx.doi.org/10.1126/science.1063127). PMID 11498575.
[76] Ito T. "Nucleosome assembly and remodelling". *Curr Top Microbiol Immunol* **274**: 1–22. PMID 12596902.
[77] Thomas J (2001). "HMG1 and 2: architectural DNA-binding proteins". *Biochem Soc Trans* **29** (Pt 4): 395–401. doi: 10.1042/BST0290395 (http://dx.doi.org/10.1042/BST0290395). PMID 11497996.
[78] Grosschedl R, Giese K, Pagel J (1994). "HMG domain proteins: architectural elements in the assembly of nucleoprotein structures". *Trends Genet* **10** (3): 94–100. doi: 10.1016/0168-9525(94)90232-1 (http://dx.doi.org/10.1016/0168-9525(94)90232-1). PMID 8178371.
[79] Iftode C, Daniely Y, Borowiec J (1999). "Replication protein A (RPA): the eukaryotic SSB". *Crit Rev Biochem Mol Biol* **34** (3): 141–80. doi: 10.1080/10409239991209255 (http://dx.doi.org/10.1080/10409239991209255). PMID 10473346.
[80] Created from PDB 1LMB (http://www.rcsb.org/pdb/explore/explore.do?structureId=1LMB)
[81] Myers L, Kornberg R (2000). "Mediator of transcriptional regulation". *Annu Rev Biochem* **69**: 729–49. doi: 10.1146/annurev.biochem.69.1.729 (http://dx.doi.org/10.1146/annurev.biochem.69.1.729). PMID 10966474.
[82] Spiegelman B, Heinrich R (2004). "Biological control through regulated transcriptional coactivators". *Cell* **119** (2): 157–67. doi: 10.1016/j.cell.2004.09.037 (http://dx.doi.org/10.1016/j.cell.2004.09.037). PMID 15479634.
[83] Li Z, Van Calcar S, Qu C, Cavenee W, Zhang M, Ren B (2003). " A global transcriptional regulatory role for c-Myc in Burkitt's lymphoma cells (http://www.pnas.org/cgi/pmidlookup?view=long&pmid=12808131)". *Proc Natl Acad Sci USA* **100** (14): 8164–9. doi: 10.1073/pnas.1332764100 (http://dx.doi.org/10.1073/pnas.1332764100). PMID 12808131. PMC: 166200 (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=166200). .
[84] Pabo C, Sauer R (1984). "Protein-DNA recognition". *Annu Rev Biochem* **53**: 293–321. doi: 10.1146/annurev.bi.53.070184.001453 (http://dx.doi.org/10.1146/annurev.bi.53.070184.001453). PMID 6236744.
[85] Created from PDB 1RVA (http://www.rcsb.org/pdb/explore/explore.do?structureId=1RVA)
[86] Bickle T, Krüger D (1993). " Biology of DNA restriction (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=372918)". *Microbiol Rev* **57** (2): 434–50. PMID 8336674.
[87] Doherty A, Suh S (2000). " Structural and mechanistic conservation in DNA ligases (http://nar.oxfordjournals.org/cgi/pmidlookup?view=long&pmid=11058099)". *Nucleic Acids Res* **28** (21): 4051–8. doi: 10.1093/nar/28.21.4051 (http://dx.doi.org/10.1093/nar/28.21.4051). PMID 11058099. PMC: 113121 (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=113121). .
[88] Schoeffler A, Berger J (2005). "Recent advances in understanding structure-function relationships in the type II topoisomerase mechanism". *Biochem Soc Trans* **33** (Pt 6): 1465–70. doi: 10.1042/BST20051465 (http://dx.doi.org/10.1042/BST20051465). PMID 16246147.
[89] Tuteja N, Tuteja R (2004). "Unraveling DNA helicases. Motif, structure, mechanism and function". *Eur J Biochem* **271** (10): 1849–63. doi: 10.1111/j.1432-1033.2004.04094.x (http://dx.doi.org/10.1111/j.1432-1033.2004.04094.x). PMID 15128295.
[90] Joyce C, Steitz T (1995). " Polymerase structures and function: variations on a theme? (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=177480)". *J Bacteriol* **177** (22): 6321–9. PMID 7592405.
[91] Hubscher U, Maga G, Spadari S (2002). "Eukaryotic DNA polymerases". *Annu Rev Biochem* **71**: 133–63. doi: 10.1146/annurev.biochem.71.090501.150041 (http://dx.doi.org/10.1146/annurev.biochem.71.090501.150041). PMID 12045093.
[92] Johnson A, O'Donnell M (2005). "Cellular DNA replicases: components and dynamics at the replication fork". *Annu Rev Biochem* **74**: 283–315. doi: 10.1146/annurev.biochem.73.011303.073859 (http://dx.doi.org/10.1146/annurev.biochem.73.011303.073859). PMID 15952889.
[93] Tarrago-Litvak L, Andréola M, Nevinsky G, Sarih-Cottin L, Litvak S (01 May 1994). " The reverse transcriptase of HIV-1: from enzymology to therapeutic intervention (http://www.fasebj.org/cgi/reprint/8/8/497)". *Faseb J* **8** (8): 497–503. PMID 7514143. .
[94] Martinez E (2002). "Multi-protein complexes in eukaryotic gene transcription". *Plant Mol Biol* **50** (6): 925–47. doi: 10.1023/A:1021258713850 (http://dx.doi.org/10.1023/A:1021258713850). PMID 12516863.
[95] Created from PDB 1M6G (http://www.rcsb.org/pdb/explore/explore.do?structureId=1M6G)

[96] Cremer T, Cremer C (2001). "Chromosome territories, nuclear architecture and gene regulation in mammalian cells". *Nat Rev Genet* **2** (4): 292–301. doi: 10.1038/35066075 (http://dx.doi.org/10.1038/35066075). PMID 11283701.
[97] Pál C, Papp B, Lercher M (2006). "An integrated view of protein evolution". *Nat Rev Genet* **7** (5): 337–48. doi: 10.1038/nrg1838 (http://dx.doi.org/10.1038/nrg1838). PMID 16619049.
[98] O'Driscoll M, Jeggo P (2006). "The role of double-strand break repair - insights from human genetics". *Nat Rev Genet* **7** (1): 45–54. doi: 10.1038/nrg1746 (http://dx.doi.org/10.1038/nrg1746). PMID 16369571.
[99] Vispé S, Defais M (1997). "Mammalian Rad51 protein: a RecA homologue with pleiotropic functions". *Biochimie* **79** (9-10): 587–92. doi: 10.1016/S0300-9084(97)82007-X (http://dx.doi.org/10.1016/S0300-9084(97)82007-X). PMID 9466696.
[100] Neale MJ, Keeney S (2006). "Clarifying the mechanics of DNA strand exchange in meiotic recombination". *Nature* **442** (7099): 153–8. doi: 10.1038/nature04885 (http://dx.doi.org/10.1038/nature04885). PMID 16838012.
[101] Dickman M, Ingleston S, Sedelnikova S, Rafferty J, Lloyd R, Grasby J, Hornby D (2002). "The RuvABC resolvasome". *Eur J Biochem* **269** (22): 5492–501. doi: 10.1046/j.1432-1033.2002.03250.x (http://dx.doi.org/10.1046/j.1432-1033.2002.03250.x). PMID 12423347.
[102] Orgel L (2004). " Prebiotic chemistry and the origin of the RNA world (http://www.crbmb.com/cgi/reprint/39/2/99.pdf)" (PDF). *Crit Rev Biochem Mol Biol* **39** (2): 99–123. doi: 10.1080/10409230490460765 (http://dx.doi.org/10.1080/10409230490460765). PMID 15217990. .
[103] Davenport R (2001). "Ribozymes. Making copies in the RNA world". *Science* **292** (5520): 1278. doi: 10.1126/science.292.5520.1278a (http://dx.doi.org/10.1126/science.292.5520.1278a). PMID 11360970.
[104] Szathmáry E (1992). " What is the optimum size for the genetic alphabet? (http://www.pnas.org/cgi/reprint/89/7/2614.pdf)" (PDF). *Proc Natl Acad Sci USA* **89** (7): 2614–8. doi: 10.1073/pnas.89.7.2614 (http://dx.doi.org/10.1073/pnas.89.7.2614). PMID 1372984. .
[105] Lindahl T (1993). "Instability and decay of the primary structure of DNA". *Nature* **362** (6422): 709–15. doi: 10.1038/362709a0 (http://dx.doi.org/10.1038/362709a0). PMID 8469282.
[106] Vreeland R, Rosenzweig W, Powers D (2000). "Isolation of a 250 million-year-old halotolerant bacterium from a primary salt crystal". *Nature* **407** (6806): 897–900. doi: 10.1038/35038060 (http://dx.doi.org/10.1038/35038060). PMID 11057666.
[107] Hebsgaard M, Phillips M, Willerslev E (2005). "Geologically ancient DNA: fact or artefact?". *Trends Microbiol* **13** (5): 212–20. doi: 10.1016/j.tim.2005.03.010 (http://dx.doi.org/10.1016/j.tim.2005.03.010). PMID 15866038.
[108] Nickle D, Learn G, Rain M, Mullins J, Mittler J (2002). "Curiously modern DNA for a "250 million-year-old" bacterium". *J Mol Evol* **54** (1): 134–7. doi: 10.1007/s00239-001-0025-x (http://dx.doi.org/10.1007/s00239-001-0025-x). PMID 11734907.
[109] Goff SP, Berg P (1976). "Construction of hybrid viruses containing SV40 and lambda phage DNA segments and their propagation in cultured monkey cells". *Cell* **9** (4 PT 2): 695–705. doi: 10.1016/0092-8674(76)90133-1 (http://dx.doi.org/10.1016/0092-8674(76)90133-1). PMID 189942.
[110] Houdebine L. "Transgenic animal models in biomedical research". *Methods Mol Biol* **360**: 163–202. PMID 17172731.
[111] Daniell H, Dhingra A (2002). "Multigene engineering: dawn of an exciting new era in biotechnology". *Curr Opin Biotechnol* **13** (2): 136–41. doi: 10.1016/S0958-1669(02)00297-5 (http://dx.doi.org/10.1016/S0958-1669(02)00297-5). PMID 11950565.
[112] Job D (2002). "Plant biotechnology in agriculture". *Biochimie* **84** (11): 1105–10. doi: 10.1016/S0300-9084(02)00013-5 (http://dx.doi.org/10.1016/S0300-9084(02)00013-5). PMID 12595138.
[113] Collins A, Morton N (1994). " Likelihood ratios for DNA identification (http://www.pnas.org/cgi/reprint/91/13/6007.pdf)" (PDF). *Proc Natl Acad Sci USA* **91** (13): 6007–11. doi: 10.1073/pnas.91.13.6007 (http://dx.doi.org/10.1073/pnas.91.13.6007). PMID 8016106. .
[114] Weir B, Triggs C, Starling L, Stowell L, Walsh K, Buckleton J (1997). "Interpreting DNA mixtures". *J Forensic Sci* **42** (2): 213–22. PMID 9068179.
[115] Jeffreys A, Wilson V, Thein S (1985). "Individual-specific 'fingerprints' of human DNA". *Nature* **316** (6023): 76–9. doi: 10.1038/316076a0 (http://dx.doi.org/10.1038/316076a0). PMID 2989708.
[116] Colin Pitchfork — first murder conviction on DNA evidence also clears the prime suspect (http://www.forensic.gov.uk/forensic_t/inside/news/list_casefiles.php?case=1) Forensic Science Service Accessed 23 December 2006
[117] "DNA Identification in Mass Fatality Incidents" (http://massfatality.dna.gov/Introduction/). National Institute of Justice. September 2006. .
[118] Baldi, Pierre; Brunak, Soren (2001), *Bioinformatics: The Machine Learning Approach*, MIT Press, ISBN 978-0-262-02506-5, OCLC 45951728 57562233 (http://worldcat.org/oclc/45951728+57562233).

[119] Gusfield, Dan. *Algorithms on Strings, Trees, and Sequences: Computer Science and Computational Biology*. Cambridge University Press, 15 January 1997. ISBN 978-0-521-58519-4.
[120] Sjölander K (2004). " Phylogenomic inference of protein molecular function: advances and challenges (http://bioinformatics.oxfordjournals.org/cgi/reprint/20/2/170)". *Bioinformatics* **20** (2): 170–9. doi: 10.1093/bioinformatics/bth021 (http://dx.doi.org/10.1093/bioinformatics/bth021). PMID 14734307. .
[121] Mount DM (2004). *Bioinformatics: Sequence and Genome Analysis* (2 ed.). Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press. ISBN 0879697121. OCLC 55106399 (http://worldcat.org/oclc/55106399).
[122] http://dx.doi.org/10.1371/journal.pbio.0020073
[123] Rothemund PW (March 2006). "Folding DNA to create nanoscale shapes and patterns". *Nature* **440** (7082): 297–302. doi: 10.1038/nature04586 (http://dx.doi.org/10.1038/nature04586). PMID 16541064.
[124] Andersen ES, Dong M, Nielsen MM, *et al.* (May 2009). "Self-assembly of a nanoscale DNA box with a controllable lid". *Nature* **459** (7243): 73–6. doi: 10.1038/nature07971 (http://dx.doi.org/10.1038/nature07971). PMID 19424153.
[125] Ishitsuka Y, Ha T (May 2009). "DNA nanotechnology: a nanomachine goes live". *Nat Nanotechnol* **4** (5): 281–2. doi: 10.1038/nnano.2009.101 (http://dx.doi.org/10.1038/nnano.2009.101). PMID 19421208.
[126] Aldaye FA, Palmer AL, Sleiman HF (September 2008). "Assembling materials with DNA as the guide". *Science* **321** (5897): 1795–9. doi: 10.1126/science.1154533 (http://dx.doi.org/10.1126/science.1154533). PMID 18818351.
[127] Wray G (2002). " Dating branches on the tree of life using DNA (http://genomebiology.com/1465-6906/3/REVIEWS0001)". *Genome Biol* **3** (1): REVIEWS0001. doi: 10.1046/j.1525-142X.1999.99010.x (http://dx.doi.org/10.1046/j.1525-142X.1999.99010.x). PMID 11806830. PMC: 150454 (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=150454). .
[128] *Lost Tribes of Israel*, NOVA, PBS airdate: 22 February 2000. Transcript available from PBS.org, (http://www.pbs.org/wgbh/nova/transcripts/2706israel.html) (last accessed on 4 March 2006)
[129] Kleiman, Yaakov. "The Cohanim/DNA Connection: The fascinating story of how DNA studies confirm an ancient biblical tradition". (http://www.aish.com/societywork/sciencenature/the_cohanim_-_dna_connection.asp) *aish.com* (January 13, 2000). Accessed 4 March 2006.
[130] Bhattacharya, Shaoni. "Killer convicted thanks to relative's DNA". (http://www.newscientist.com/article.ns?id=dn4908) *newscientist.com* (20 April 2004). Accessed 22 December 06
[131] Dahm R (January 2008). "Discovering DNA: Friedrich Miescher and the early years of nucleic acid research". *Hum. Genet.* **122** (6): 565–81. doi: 10.1007/s00439-007-0433-0 (http://dx.doi.org/10.1007/s00439-007-0433-0). PMID 17901982.
[132] Levene P, (01 December 1919). " The structure of yeast nucleic acid (http://www.jbc.org/cgi/reprint/40/2/415)". *J Biol Chem* **40** (2): 415–24. .
[133] Astbury W, (1947). "Nucleic acid". *Symp. SOC. Exp. Bbl* **1** (66).
[134] Lorenz MG, Wackernagel W (01 September 1994). " Bacterial gene transfer by natural genetic transformation in the environment (http://mmbr.asm.org/cgi/pmidlookup?view=long&pmid=7968924)". *Microbiol. Rev.* **58** (3): 563–602. PMID 7968924. PMC: 372978 (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=372978). .
[135] Avery O, MacLeod C, McCarty M (1944). " Studies on the chemical nature of the substance inducing transformation of pneumococcal types. Inductions of transformation by a desoxyribonucleic acid fraction isolated from pneumococcus type III (http://www.jem.org/cgi/reprint/149/2/297)". *J Exp Med* **79** (2): 137–158. doi: 10.1084/jem.79.2.137 (http://dx.doi.org/10.1084/jem.79.2.137). .
[136] Hershey A, Chase M (1952). " Independent functions of viral protein and nucleic acid in growth of bacteriophage (http://www.jgp.org/cgi/reprint/36/1/39.pdf)" (PDF). *J Gen Physiol* **36** (1): 39–56. doi: 10.1085/jgp.36.1.39 (http://dx.doi.org/10.1085/jgp.36.1.39). PMID 12981234. .
[137] The B-DNA X-ray pattern on the right of this linked image (http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/dna/pictures/sci9.001.5.html) was obtained by Rosalind Franklin and Raymond Gosling in May 1952 at high hydration levels of DNA and it has been labeled as "Photo 51"
[138] Nature Archives Double Helix of DNA: 50 Years (http://www.nature.com/nature/dna50/archive.html)
[139] Original X-ray diffraction image (http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/dna/pictures/franklin-typeBphoto.html)
[140] The Nobel Prize in Physiology or Medicine 1962 (http://nobelprize.org/nobel_prizes/medicine/laureates/1962/) Nobelprize .org Accessed 22 December 06
[141] Brenda Maddox (23 January 2003). " The double helix and the 'wronged heroine' (http://www.biomath.nyu.edu/index/course/hw_articles/nature4.pdf)" (PDF). *Nature* **421**: 407–408. doi: 10.1038/nature01399 (http://dx.doi.org/10.1038/nature01399). PMID 12540909. .
[142] Crick, F.H.C. On degenerate templates and the adaptor hypothesis (PDF). (http://genome.wellcome.ac.uk/assets/wtx030893.pdf) genome.wellcome.ac.uk (Lecture, 1955). Accessed 22 December 2006

[143] Meselson M, Stahl F (1958). "The replication of DNA in *Escherichia coli*". *Proc Natl Acad Sci USA* **44** (7): 671–82. doi: 10.1073/pnas.44.7.671 (http://dx.doi.org/10.1073/pnas.44.7.671). PMID 16590258.
[144] The Nobel Prize in Physiology or Medicine 1968 (http://nobelprize.org/nobel_prizes/medicine/laureates/1968/) Nobelprize.org Accessed 22 December 06
[145] http://proteopedia.org/wiki/index.php/DNA

Further reading

- Calladine, Chris R.; Drew, Horace R.; Luisi, Ben F. and Travers, Andrew A. (2003). *Understanding DNA: the molecule & how it works*. Amsterdam: Elsevier Academic Press. ISBN 0-12-155089-3.
- Dennis, Carina; Julie Clayton (2003). *50 years of DNA*. Basingstoke: Palgrave Macmillan. ISBN 1-4039-1479-6.
- Judson, Horace Freeland (1996). *The eighth day of creation: makers of the revolution in biology*. Plainview, N.Y: CSHL Press. ISBN 0-87969-478-5.
- Olby, Robert C. (1994). *The path to the double helix: the discovery of DNA*. New York: Dover Publications. ISBN 0-486-68117-3., first published in October 1974 by MacMillan, with foreword by Francis Crick;the definitive DNA textbook,revised in 1994 with a 9 page postscript.
- Olby, Robert C. (2009). *Francis Crick: A Biography*. Plainview, N.Y: Cold Spring Harbor Laboratory Press. ISBN 0-87969-798-9.
- Ridley, Matt (2006). *Francis Crick: discoverer of the genetic code*. [Ashland, OH: Eminent Lives, Atlas Books. ISBN 0-06-082333-X.
- Berry, Andrew; Watson, James D. (2003). *DNA: the secret of life*. New York: Alfred A. Knopf. ISBN 0-375-41546-7.
- Stent, Gunther Siegmund; Watson, James D. (1980). *The double helix: a personal account of the discovery of the structure of DNA*. New York: Norton. ISBN 0-393-95075-1.
- Wilkins, Maurice (2003). *The third man of the double helix the autobiography of Maurice Wilkins*. Cambridge, Eng: University Press. ISBN 0-19-860665-6.

External links

- DNA (http://www.dmoz.org/Science/Biology/Biochemistry_and_Molecular_Biology/Biomolecules/Nucleic_Acids/DNA//) at the Open Directory Project
- DNA binding site prediction on protein (http://pipe.scs.fsu.edu/displar.html)
- DNA coiling to form chromosomes (http://biostudio.com/c_ education mac.htm)
- DNA from the Beginning (http://www.dnaftb.org/dnaftb/) Another DNA Learning Center site on DNA, genes, and heredity from Mendel to the human genome project.
- DNA Lab, demonstrates how to extract DNA from wheat using readily available equipment and supplies. (http://ca.youtube.com/watch?v=iyb7fwduuGM)
- DNA the Double Helix Game (http://nobelprize.org/educational_games/medicine/dna_double_helix/) From the official Nobel Prize web site
- DNA under electron microscope (http://www.fidelitysystems.com/Unlinked_DNA.html)
- Dolan DNA Learning Center (http://www.dnalc.org/)
- Double Helix: 50 years of DNA (http://www.nature.com/nature/dna50/archive.html), *Nature*
- Double Helix 1953–2003 (http://www.ncbe.reading.ac.uk/DNA50/) National Centre for Biotechnology Education

- Francis Crick and James Watson talking on the BBC in 1962, 1972, and 1974 (http://www.bbc.co.uk/bbcfour/audiointerviews/profilepages/crickwatson1.shtml)
- Genetic Education Modules for Teachers (http://www.genome.gov/10506718) — *DNA from the Beginning* Study Guide
- Guide to DNA cloning (http://www.blackwellpublishing.com/trun/artwork/Animations/cloningexp/cloningexp.html)
- Olby R (January 2003). " Quiet debut for the double helix (http://chem-faculty.ucsd.edu/joseph/CHEM13/DNA1.pdf)". *Nature* **421** (6921): 402–5. doi: 10.1038/nature01397 (http://dx.doi.org/10.1038/nature01397). PMID 12540907. http://chem-faculty.ucsd.edu/joseph/CHEM13/DNA1.pdf.
- PDB Molecule of the Month *pdb23_1 (http://www.rcsb.org/pdb/static.do?p=education_discussion/molecule_of_the_month/pdb23_1.html)*
- Rosalind Franklin's contributions to the study of DNA (http://mason.gmu.edu/~emoody/rfranklin.html)
- The Register of Francis Crick Personal Papers 1938 - 2007 (http://orpheus.ucsd.edu/speccoll/testing/html/mss0660a.html#abstract) at Mandeville Special Collections Library, Geisel Library, University of California, San Diego
- U.S. National DNA Day (http://www.genome.gov/10506367) — watch videos and participate in real-time chat with top scientists
- " Clue to chemistry of heredity found (http://www.nytimes.com/packages/pdf/science/dna-article.pdf)". *The New York Times*. Saturday, June 13, 1953. http://www.nytimes.com/packages/pdf/science/dna-article.pdf. The first American newspaper coverage of the discovery of the DNA structure.
- (http://www.elmhurst.edu/~chm/vchembook/581nucleotides.html)

DNA structure

DNA structure shows a variety of forms, both double-stranded and single-stranded. The mechanical properties of DNA, which are directly related to its structure, are a significant problem for cells. Every process which binds or reads → DNA is able to use or modify the mechanical properties of DNA for purposes of recognition, packaging and modification. The extreme length (a chromosome may contain a 10 cm long DNA strand), relative rigidity and helical structure of DNA has led to the evolution of histones and of enzymes such as topoisomerases and helicases to manage a cell's DNA. The properties of DNA are closely related to its molecular structure and sequence, particularly the weakness of the hydrogen bonds and electronic interactions that hold strands of DNA together compared to the strength of the bonds within each strand.

Experimental techniques which can directly measure the mechanical properties of DNA are relatively new, and high-resolution visualization in solution is often difficult. Nevertheless, scientists have uncovered large amount of data on the mechanical properties of this polymer, and the implications of DNA's mechanical properties on cellular processes is a topic of active current research.

It is important to note the DNA found in many cells can be macroscopic in length - a few centimetres long for each human chromosome. Consequently, cells must compact or "package" DNA to carry it within them. In eukaryotes this is carried by spool-like proteins known as histones, around which DNA winds. It is the further compaction of this DNA-protein complex which produces the well known mitotic eukaryotic chromosomes.

Structure determination

DNA structures can be determined using either nuclear magnetic resonance spectroscopy or X-ray crystallography. The first published reports of A-DNA X-ray diffraction patterns--and also B-DNA—employed analyses based on Patterson transforms that provided only a limited amount of structural information for oriented fibers of DNA isolated from calf thymus.[1] [29] An alternate analysis was then proposed by Wilkins et al. in 1953 for B-DNA X-ray diffraction/scattering patterns of hydrated, bacterial oriented DNA fibers and trout sperm heads in terms of squares of Bessel functions.[30] Although the `B-DNA form' is most common under the conditions found in cells,[2] it is not a well-defined conformation but a family or fuzzy set of DNA-conformations that occur at the high hydration levels present in a wide variety of living cells.[3] Their corresponding X-ray diffraction & scattering patterns are characteristic of molecular paracrystals with a significant degree of disorder (>20%)[4] [5] , and concomitantly the structure is not tractable using only the standard analysis.

On the other hand, the standard analysis, involving only Fourier transforms of Bessel functions[6] and DNA molecular models, is still routinely employed for the analysis of A-DNA and Z-DNA X-ray diffraction patterns.[7]

Base pair geometry

The geometry of a base, or base pair step can be characterized by 6 coordinates: Shift, Slide, Rise, Tilt, Roll, and Twist. These values precisely define the location and orientation in space of every base or base pair in a DNA molecule relative to its predecessor along the axis of the helix. Together, they characterize the helical structure of the molecule. In regions of DNA where the "normal" structure is disrupted the change in these values can be used to describe such disruption.

For each base pair, considered relative to its predecessor[8] [9] [10] :

Shear

Stretch

Stagger

Buckle

Propeller twist

Rotation of one base with respect to the other in the same base pair.

Opening

Shift

displacement along an axis in the base-pair plane perpendicular to the first, directed from the minor to the major groove.

Slide

displacement along an axis in the plane of the base pair directed from one strand to the other.

Rise

displacement along the helix axis.

Tilt

rotation around this axis.

Roll

rotation around this axis.

Twist

rotation around the helix axis.

x-displacement

y-displacement

inclination

tip

pitch

the number of base pairs per complete turn of the helix

Rise and twist determine the handedness and pitch of the helix. The other coordinates, by contrast, can be zero. Slide and shift are typically small in B-DNA, but are substantial in A- and Z-DNA. Roll and tilt make successive base pairs less parallel, and are typically small. A diagram [11] of these coordinates can be found in 3DNA [12] website.

Note that "tilt" has often been used differently in the scientific literature, referring to the deviation of the first, inter-strand base-pair axis from perpendicularity to the helix axis. This

corresponds to slide between a succession of base pairs, and in helix-based coordinates is properly termed "inclination".

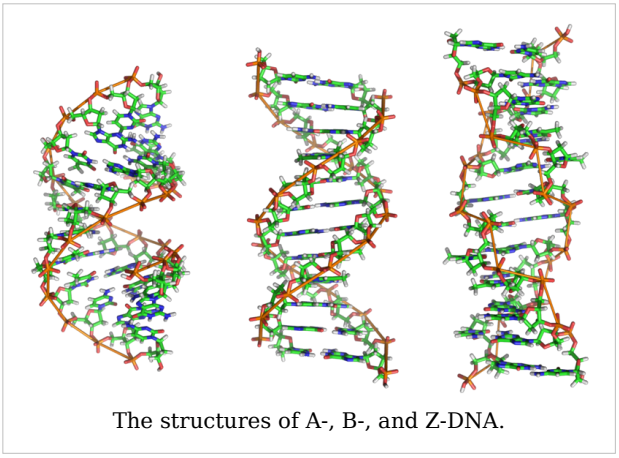
DNA helix geometries

Three DNA conformations are believed to be found in nature, A-DNA, B-DNA, and Z-DNA. The "B" form described by James D. Watson and Francis Crick is believed to predominate in cells[13] . It is 23.7 Å wide and extends 34 Å per 10 bp of sequence. The double helix makes one complete turn about its axis every 10.4-10.5 base pairs in solution. This frequency of twist (known as the helical *pitch*) depends largely on stacking forces that each base exerts on its neighbours in the chain.

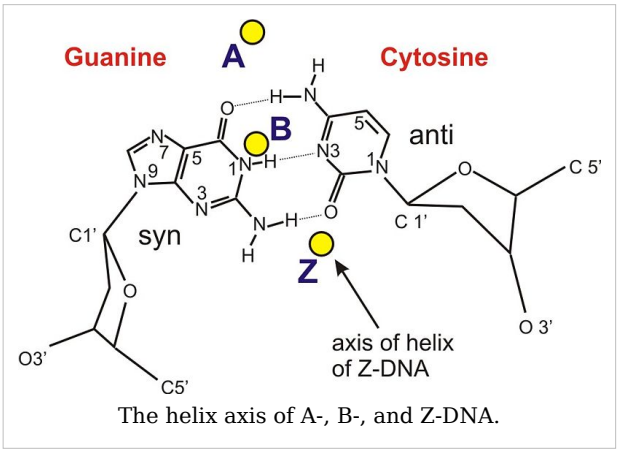
Other conformations are possible; A-DNA, B-DNA, C-DNA, D-DNA[14] , E-DNA[15] , L-DNA(enantiomeric form of D-DNA)[14] , P-DNA[16] , S-DNA, Z-DNA, etc. have been described so far.[17] In fact, only the letters F, Q, U, V, and Y are now available to describe any new DNA structure that may appear in the future.[18] [19] However, most of these forms have been created synthetically and have not been observed in naturally occurring biological systems. Also note the triple-stranded DNA possibility.

A-and Z-DNA

A-DNA and Z-DNA differ significantly in their geometry and dimensions to B-DNA, although still form helical structures. The A form appears likely to occur only in dehydrated samples of DNA, such as those used in crystallographic experiments, and possibly in hybrid pairings of DNA and RNA strands. Segments of DNA that cells have methylated for regulatory purposes may adopt the Z geometry, in which the strands turn about the helical axis the opposite way to A-DNA and B-DNA. There is also evidence of protein-DNA complexes forming Z-DNA structures.



The structures of A-, B-, and Z-DNA.



The helix axis of A-, B-, and Z-DNA.

Geometry attribute	A-DNA	B-DNA	Z-DNA
Helix sense	right-handed	right-handed	left-handed
Repeating unit	1 bp	1 bp	2 bp
Rotation/bp	33.6°	35.9°	60°/2bp
Mean bp/turn	10.7	10.0	12
Inclination of bp to axis	+19°	-1.2°	-9°
Rise/bp along axis	2.3 Å	3.32 Å	3.8 Å

Pitch/turn of helix	24.6 Å	33.2 Å	45.6 Å
Mean propeller twist	+18°	+16°	0°
Glycosyl angle	anti	anti	**C**: anti, **G**: syn
Sugar pucker	C3'-endo	C2'-endo	**C**: C2'-endo, **G**: C2'-exo
Diameter	25.5 Å	23.7 Å	18.4 Å

Supercoiled DNA

The B form of the DNA helix twists 360° per 10.4-10.5 bp in the absence of torsional strain. But many molecular biological processes can induce torsional strain. A DNA segment with excess or insufficient helical twisting is referred to, respectively, as positively or negatively "supercoiled". DNA *in vivo* is typically negatively supercoiled, which facilitates the unwinding (melting) of the double-helix required for RNA transcription.

Non-helical forms

Other non-double helical forms of DNA have been described, for example side-by-side (SBS) and triple helical configurations. Single stranded DNA may exist *in statu nascendi* or as thermally induced despiralized DNA.

DNA bending

DNA is a relatively rigid polymer, typically modelled as a worm-like chain. It has three significant degrees of freedom; bending, twisting and compression, each of which cause particular limitations on what is possible with DNA within a cell. Twisting/torsional stiffness is important for the circularisation of DNA and the orientation of DNA bound proteins relative to each other and bending/axial stiffness is important for DNA wrapping and circularisation and protein interactions. Compression/extension is relatively unimportant in the absence of high tension.

Persistence length/Axial stiffness

Example sequences and their persistence lengths (B DNA)

Sequence	Persistence Length /base pairs
Random	154±10
$(\mathbf{CA})_{\text{repeat}}$	133±10
$(\mathbf{CAG})_{\text{repeat}}$	124±10
$(\mathbf{TATA})_{\text{repeat}}$	137±10

DNA in solution does not take a rigid structure but is continually changing conformation due to thermal vibration and collisions with water molecules, which makes classical measures of rigidity impossible. Hence, the bending stiffness of DNA is measured by the persistence length, defined as:

"The length of DNA over which the time-averaged orientation of the polymer becomes uncorrelated by a factor of *e*."

This value may be directly measured using an atomic force microscope to directly image DNA molecules of various lengths. In aqueous solution the average persistence length is 46-50 nm or 140-150 base pairs (the diameter of DNA is 2 nm), although can vary significantly. This makes DNA a moderately stiff molecule.

The persistence length of a section of DNA is somewhat dependent on its sequence, and this can cause significant variation. The variation is largely due to base stacking energies and the residues which extend into the minor and major grooves.

Models for DNA bending

Stacking stability of base steps (B DNA)

Step	Stacking ΔG /kcal mol^{-1}
T A	-0.19
T G or **C A**	-0.55
C G	-0.91
A G or **C T**	-1.06
A A or **T T**	-1.11
A T	-1.34
G A or **T C**	-1.43
C C or **G G**	-1.44
A C or **G T**	-1.81
G C	-2.17

The entropic flexibility of DNA is remarkably consistent with standard polymer physics models such as the *Kratky-Porod* worm-like chain model. Consistent with the worm-like chain model is the observation that bending DNA is also described by Hooke's law at very small (sub-piconewton) forces. However for DNA segments less than the persistence length, the bending force is approximately constant and behaviour deviates from the worm-like chain predictions.

This effect results in unusual ease in circularising small DNA molecules and a higher probability of finding highly bent sections of DNA.

Bending preference

DNA molecules often have a preferred direction to bend, ie. anisotropic bending. This is, again, due to the properties of the bases which make up the DNA sequence - a random sequence will have no preferred bend direction, i.e. isotropic bending.

Preferred DNA bend direction is determined by the stability of stacking each base on top of the next. If unstable base stacking steps are always found on one side of the DNA helix then the DNA will preferentially bend away from that direction. As bend angle increases then steric hindrances and ability to roll the residues relative to each other also play a role, especially in the minor groove. **A** and **T** residues will be preferentially be found in the minor

grooves on the inside of bends. This effect is particularly seen in DNA-protein binding where tight DNA bending is induced, such as in nucleosome particles. See base step distortions above.

DNA molecules with exceptional bending preference can become intrinsically bent. This was first observed in trypanosomatid kinetoplast DNA. Typical sequences which cause this contain stretches of 4-6 **T** and **A** residues separated by **G** and **C** rich sections which keep the A and T residues in phase with the minor groove on one side of the molecule. For example:

```
 |                 |                   |                   |
                  |                   |
G A T T C C C A A A A A T G T C A A A A A A T A G G C A A A A A A T G C
 C A A A A A A T C C C A A A C
```

The intrinsically bent structure is induced by the 'propeller twist' of base pairs relative to each other allowing unusual bifurcated Hydrogen-bonds between base steps. At higher temperatures this structure, and so the intrinsic bend, is lost.

All DNA which bends anisotropically has, on average, a longer persistence length and greater axial stiffness. This increased rigidity is required to prevent random bending which would make the molecule act isotropically.

DNA circularisation

DNA circularisation depends on both the axial (bending) stiffness and torsional (rotational) stiffness of the molecule. For a DNA molecule to successfully circularise it must be long enough to easily bend into the full circle and must have the correct number of bases so the ends are in the correct rotation to allow bonding to occur. The optimum length for circularisation of DNA is around 400 base pairs (136 nm), with an integral number of turns of the DNA helix, i.e. multiples of 10.4 base pairs. Having a non integral number of turns presents a significant energy barrier for circularisation, for example a 10.4 x 30 = 312 base pair molecule will circularise hundreds of times faster than 10.4 x 30.5 ≈ 317 base pair molecule.

DNA stretching

Longer stretches of DNA are entropically elastic under tension. When DNA is in solution, it undergoes continuous structural variations due to the energy available in the solvent. This is due to the thermal vibration of the molecule combined with continual collisions with water molecules. For entropic reasons, more compact relaxed states are thermally accessible than stretched out states, and so DNA molecules are almost universally found in a tangled relaxed layouts. For this reason, a single molecule of DNA will stretch under a force, straightening it out. Using optical tweezers, the entropic stretching behavior of DNA has been studied and analyzed from a polymer physics perspective, and it has been found that DNA behaves largely like the *Kratky-Porod* worm-like chain model under physiologically accessible energy scales.

Under sufficient tension and positive torque, DNA is thought to undergo a phase transition with the bases splaying outwards and the phosphates moving to the middle. This proposed structure for overstretched DNA has been called "P-form DNA," in honor of Linus Pauling who originally presented it as a possible structure of DNA[16]

The mechanical properties DNA under compression have not been characterized due to experimental difficulties in preventing the polymer from bending under the compressive force.

DNA melting

Melting stability of base steps (B DNA)

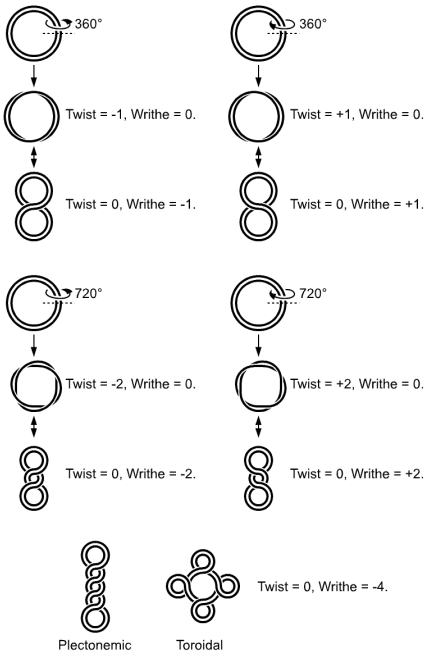
Step	Melting ΔG /Kcal mol^{-1}
T A	-0.12
T G or **C A**	-0.78
C G	-1.44
A G or **C T**	-1.29
A A or **T T**	-1.04
A T	-1.27
G A or **T C**	-1.66
C C or **G G**	-1.97
A C or **G T**	-2.04
G C	-2.70

DNA melting is the process by which the interactions between the strands of the double helix are broken, separating the two strands of DNA. These bonds are weak, easily separated by gentle heating, enzymes, or physical force. DNA melting preferentially occurs at certain points in the DNA.[20] **T** and **A** rich sequences are more easily melted than **C** and **G** rich regions. Particular base steps are also susceptible to DNA melting, particularly **T A** and **T G** base steps.[21] These mechanical features are reflected by the use of sequences such as **TATAA** at the start of many genes to assist RNA polymerase in melting the DNA for transcription.

Strand separation by gentle heating, as used in PCR, is simple providing the molecules have fewer than about 10,000 base pairs (10 kilobase pairs, or 10 kbp). The intertwining of the DNA strands makes long segments difficult to separate. The cell avoids this problem by allowing its DNA-melting enzymes (helicases) to work concurrently with topoisomerases, which can chemically cleave the phosphate backbone of one of the strands so that it can swivel around the other. Helicases unwind the strands to facilitate the advance of sequence-reading enzymes such as DNA polymerase.

DNA topology

Within the cell most DNA is topologically restricted. DNA is typically found in closed loops (such as plasmids in prokaryotes) which are topologically closed, or as very long molecules whose diffusion coefficients produce effectively topologically closed domains. Linear sections of DNA are also commonly bound to proteins or physical structures (such as membranes) to form closed topological loops.



Supercoiled structure of circular DNA molecules with low writhe. Note that the helical nature of the DNA duplex is omitted for clarity.

Francis Crick was one of the first to propose the importance of linking numbers when considering DNA supercoils. In a paper published in 1976, Crick outlined the problem as follows:

> In considering supercoils formed by closed double-stranded molecules of DNA certain mathematical concepts, such as the linking number and the twist, are needed. The meaning of these for a closed ribbon is explained and also that of the writhing number of a closed curve. Some simple examples are given, some of which may be relevant to the structure of chromatin.[22]

Analysis of DNA topology uses three values:

L = linking number - the number of times one DNA strand wraps around the other. It is an integer for a closed loop and constant for a closed topological domain.

T = twist - total number of turns in the double stranded DNA helix. This will normally try to be equal to the number turns a DNA molecule will make while free in solution, ie. number of bases/10.4.

W = writhe - number of turns of the double stranded DNA helix around the superhelical axis

$$L = T + W \text{ and } \Delta L = \Delta T + \Delta W$$

Any change of T in a closed topological domain must be balanced by a change in W, and vice versa. This results in higher order structure of DNA. A circular DNA molecule with a writhe of 0 will be circular. If the twist of this molecule is subsequently increased or decreased by supercoiling then the writhe will be appropriately altered, making the molecule undergo plectonemic or toroidal superhelical coiling.

When the ends of a piece of double stranded helical DNA are joined so that it forms a circle the strands are topologically knotted. This means the single strands cannot be separated any process that does not involve breaking a strand (such as heating). The task of un-knotting topologically linked strands of DNA falls to enzymes known as topoisomerases. These enzymes are dedicated to un-knotting circular DNA by cleaving one or both strands so that another double or single stranded segment can pass through. This un-knotting is required for the replication of circular DNA and various types of recombination in linear DNA which have similar topological constraints.

The linking number paradox

For many years, the origin of residual supercoiling in eukaryotic genomes remained unclear. This topological puzzle was referred to by some as the "linking number paradox".[23] However, when experimentally determined structures of the nucleosome displayed an overtwisted left-handed wrap of DNA around the histone octamer[24] [25] , this "paradox" was solved.

See also

- → DNA nanotechnology
- → Molecular models of DNA

References

[1] Franklin, R.E. and Gosling, R.G. received 6 March 1953. *Acta Cryst.* (1953). **6**, 673: The Structure of Sodium Thymonucleate Fibres I. The Influence of Water Content.; also *Acta Cryst.* **6**, 678: The Structure of Sodium Thymonucleate Fibres II. The Cylindrically Symmetrical Patterson Function.

[2] Leslie AG, Arnott S, Chandrasekaran R, Ratliff RL (1980). "Polymorphism of DNA double helices". *J. Mol. Biol.* **143** (1): 49–72. doi: 10.1016/0022-2836(80)90124-2 (http://dx.doi.org/10.1016/0022-2836(80)90124-2). PMID 7441761.

[3] Baianu, I.C. (1980). "Structural Order and Partial Disorder in Biological systems". *Bull. Math. Biol.* **42** (4): 464–468. doi: 10.1016/0022-2836(80)90124-2 (http://dx.doi.org/10.1016/0022-2836(80)90124-2).

[4] Hosemann R., Bagchi R.N., *Direct analysis of diffraction by matter*, North-Holland Publs., Amsterdam – New York, 1962

[5] Baianu I.C., X-ray scattering by partially disordered membrane systems, *Acta Cryst. A*, **34** (1978), 751–753.

[6] Bessel functions and diffraction by helical structures (http://planetphysics.org/encyclopedia/BesselFunctionsAndTheirApplicationsToDiffractionByHelicalStructures.html)

[7] X-Ray Diffraction Patterns of Double-Helical Deoxyribonucleic Acid (DNA) Crystals (http://planetphysics.org/encyclopedia/BesselFunctionsApplicationsToDiffractionByHelicalStructures.html)

[8] Dickerson RE (1989). "Definitions and nomenclature of nucleic acid structure components". *Nucleic Acids Res* **17** (5): 1797–1803. doi: 10.1093/nar/17.5.1797 (http://dx.doi.org/10.1093/nar/17.5.1797). PMID 2928107.

[9] Lu XJ, Olson WK (1999). "Resolving the discrepancies among nucleic acid conformational analyses". *J Mol Biol* **285** (4): 1563–1575. doi: 10.1006/jmbi.1998.2390 (http://dx.doi.org/10.1006/jmbi.1998.2390). PMID 9917397.

[10] Olson WK, Bansal M, Burley SK, Dickerson RE, Gerstein M, Harvey SC, Heinemann U, Lu XJ, Neidle S, Shakked Z, Sklenar H, Suzuki M, Tung CS, Westhof E, Wolberger C, Berman HM (2001). "A standard reference frame for the description of nucleic acid base-pair geometry". *J Mol Biol* **313** (1): 229–237. doi: 10.1006/jmbi.2001.4987 (http://dx.doi.org/10.1006/jmbi.2001.4987). PMID 11601858.

[11] http://rutchem.rutgers.edu/~xiangjun/3DNA/images/bp_step_hel.gif

[12] http://rutchem.rutgers.edu/~xiangjun/3DNA/examples.html

[13] Richmond, et al. (2003). "The structure of DNA in the nucleosome core". *Nature* **423**: 145–150. doi: 10.1038/nature01595 (http://dx.doi.org/10.1038/nature01595). PMID 12736678.

[14] Hayashi G, Hagihara M, Nakatani K (2005). "Application of L-DNA as a molecular tag". *Nucleic Acids Symp Ser (Oxf)* **49**: 261-262. PMID 17150733.

[15] Vargason JM, Eichman BF, Ho PS (2000). "The extended and eccentric E-DNA structure induced by cytosine methylation or bromination". *Nature Structural Biology* **7**: 758–761. doi: 10.1038/78985 (http://dx.doi.org/10.1038/78985).

[16] Allemand, et al. (1998). "Stretched and overwound DNA forms a Pauling-like structure with exposed bases". *PNAS* **24**: 14152–14157. doi: 10.1073/pnas.95.24.14152 (http://dx.doi.org/10.1073/pnas.95.24.14152). PMID 9826669.

[17] List of 55 fiber structures (http://rutchem.rutgers.edu/~xiangjun/3DNA/misc/fiber_model.txt)

[18] Bansal M (2003). "DNA structure: Revisiting the Watson-Crick double helix". *Current Science* **85** (11): 1556-1563.

[19] Ghosh A, Bansal M (2003). "A glossary of DNA structures from A to Z". *Acta Cryst* **D59**: 620-626. doi: 10.1107/S0907444903003251 (http://dx.doi.org/10.1107/S0907444903003251).

[20] Breslauer KJ, Frank R, Blöcker H, Marky LA (1986). "Predicting DNA duplex stability from the base sequence". *PNAS* **83** (11): 3746-3750. PMID 3459152.
[21] Richard Owczarzy (2008-08-28). "DNA melting temperature - How to calculate it?" (http://www.owczarzy.net/tm.htm). *High-throughput DNA biophysics*. owczarzy.net. . Retrieved on 2008-10-02.
[22] Crick FH (1976). "Linking numbers and nucleosomes". *Proc Natl Acad Sci USA* **73** (8): 2639–43. doi: 10.1073/pnas.73.8.2639 (http://dx.doi.org/10.1073/pnas.73.8.2639). PMID 1066673.
[23] Prunell A (1998). "A topological approach to nucleosome structure and dynamics: the linking number paradox and other issues". *Biophys J* **74** (5): 2531–2544. PMID 9591679.
[24] Luger K, Mader AW, Richmond RK, Sargent DF, Richmond TJ (1997). "Crystal structure of the nucleosome core particle at 2.8 A resolution". *Nature* **389** (6648): 251-260. doi: 10.1038/38444 (http://dx.doi.org/10.1038/38444). PMID 9305837.
[25] Davey CA, Sargent DF, Luger K, Maeder AW, Richmond TJ (2002). "Solvent mediated interactions in the structure of the nucleosome core particle at 1.9 Å resolution". *Journal of Molecular Biology* **319** (5): 1097-1113. doi: 10.1016/S0022-2836(02)00386-8 (http://dx.doi.org/10.1016/S0022-2836(02)00386-8). PMID 12079350.

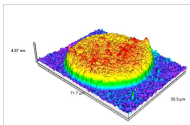
External links

- MDDNA: Structural Bioinformatics of DNA (http://humphry.chem.wesleyan.edu:8080/MDDNA/)
- Ascalaph DNA (http://www.agilemolecule.com/Ascalaph/Ascalaph_DNA.html) — Commercial software for DNA modeling
- DNAlive: a web interface to compute DNA physical properties (http://mmb.pcb.ub.es/DNAlive). Also allows cross-linking of the results with the UCSC Genome browser and DNA dynamics.
- DiProDB: Dinucleotide Property Database (http://diprodb.fli-leibniz.de). The database is designed to collect and analyse thermodynamic, structural and other dinucleotide properties.

Molecular models of DNA

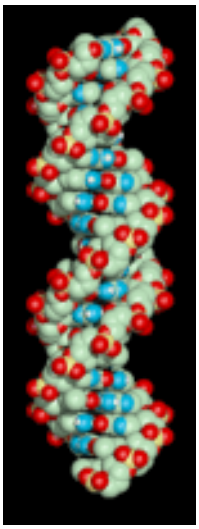
Molecular models of DNA structures are representations of the molecular geometry and topology of Deoxyribonucleic acid (→ DNA) molecules using one of several means, such as: closely packed spheres (CPK models) made of plastic, metal wires for 'skeletal models', graphic computations and animations by computers, artistic rendering, and so on, with the aim of simplifying and presenting the essential, physical and chemical, properties of DNA molecular structures either *in vivo* or *in vitro*. Computer molecular models also allow animations and molecular dynamics simulations that are very important for understanding how DNA functions *in vivo*. Thus, an old standing dynamic problem is how DNA "self-replication" takes place in living cells that should involve transient uncoiling of supercoiled DNA fibers. Although DNA consists of relatively rigid, very large elongated biopolymer molecules called "fibers" or chains (that are made of repeating nucleotide units of four basic types, attached to deoxyribose and phosphate groups), its molecular structure *in vivo* undergoes dynamic configuration changes that involve dynamically attached water molecules and ions. Supercoiling, packing with histones in chromosome structures, and other such supramolecular aspects also involve *in vivo* DNA topology which is even more complex than DNA molecular geometry, thus turning molecular modeling of DNA into an especially challenging problem for both molecular biologists and biotechnologists. Like other large molecules and biopolymers, DNA often exists in multiple stable geometries (that is, it exhibits conformational isomerism) and configurational, quantum states which are close to each other in energy on the potential energy surface of the DNA molecule. Such geometries can also be computed, at least in principle, by employing *ab initio* quantum chemistry methods that have high accuracy for small molecules. Such quantum geometries define an important class of *ab initio* molecular models of DNA whose exploration has barely started.

In an interesting twist of roles, the DNA molecule itself was proposed to be utilized for quantum computing. Both DNA nanostructures as well as DNA 'computing' biochips have been built (see biochip image at right).



DNA computing biochip:3D

The more advanced, computer-based molecular models of DNA involve molecular dynamics simulations as well as quantum mechanical computations of vibro-rotations, delocalized molecular orbitals (MOs), electric dipole moments, hydrogen-bonding, and so on.



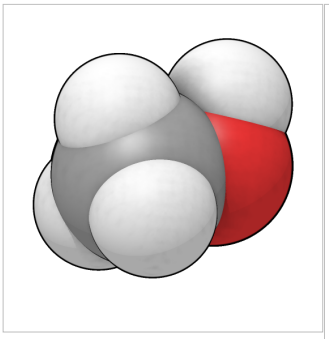
Spinning DNA generic model.

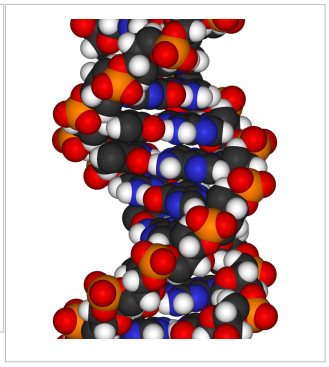
Importance

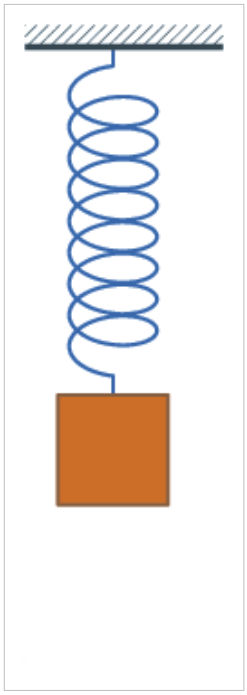
From the very early stages of structural studies of DNA by X-ray diffraction and biochemical means, molecular models such as the Watson-Crick double-helix model were successfully employed to solve the 'puzzle' of DNA structure, and also find how the latter relates to its key functions in living cells. The first high quality X-ray diffraction patterns of A-DNA were reported by Rosalind Franklin and Raymond Gosling in 1953[1] . The first calculations of the Fourier transform of an atomic helix were reported one year earlier by Cochran, Crick and Vand [2] , and were followed in 1953 by the computation of the Fourier transform of a coiled-coil by Crick[3] . The first reports of a double-helix molecular model of B-DNA structure were made by Watson and Crick in 1953[4] [5] . Last-but-not-least, Maurice F. Wilkins, A. Stokes and H.R. Wilson, reported the first X-ray patterns of *in vivo* B-DNA in partially oriented salmon sperm heads [30] . The development of the first correct double-helix molecular model of DNA by Crick and Watson may not have been possible without the biochemical evidence for the nucleotide base-pairing ([A---T]; [C---G]), or Chargaff's rules[6] [7] [8] [9] [10] [11] .

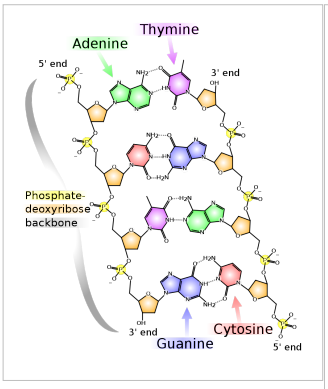
Examples of DNA molecular models

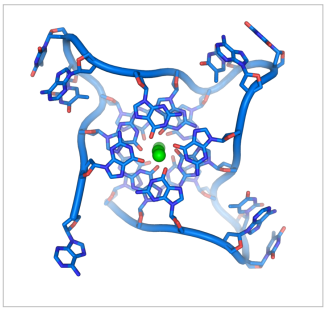
Animated molecular models allow one to visually explore the three-dimensional (3D) structure of DNA. The first DNA model is a space-filling, or CPK, model of the DNA double-helix whereas the third is an animated wire, or skeletal type, molecular model of DNA. The last two DNA molecular models in this series depict quadruplex DNA [12] that may be involved in certain cancers[13] [14] . The last figure on this panel is a molecular model of hydrogen bonds between water molecules in ice that are similar to those found in DNA.

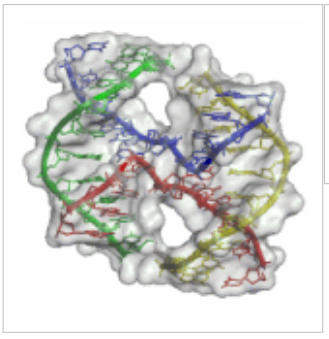


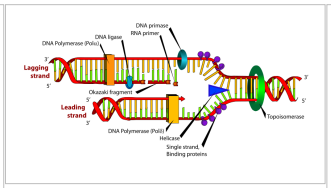


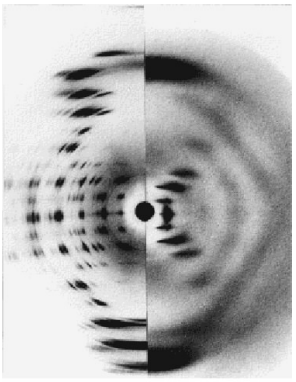


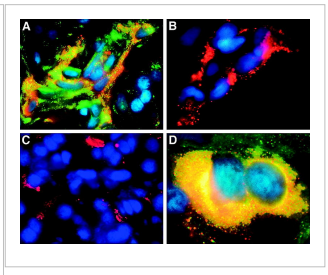

Thymine
Adenine
5' end
3' end
Phosphate-
deoxyribose
backbone
3' end
Guanine
Cytosine
5' end

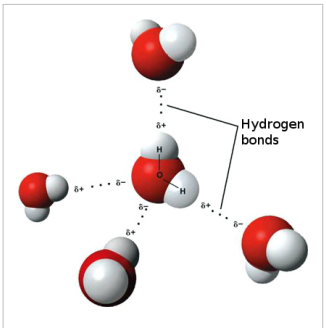




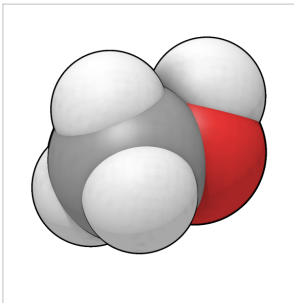

Lagging strand
Leading strand
DNA Polymerase (Pol I)
DNA ligase
DNA primase
RNA primer
Okazaki fragment
DNA Polymerase (Pol III)
Helicase
Single strand, Binding proteins
Topoisomerase


A-DNA
B-DNA


A
B
C
D



- Spacefilling model or CPK model - a molecule is represented by overlapping spheres representing the atoms.

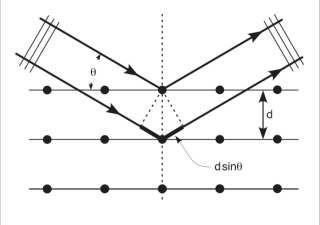


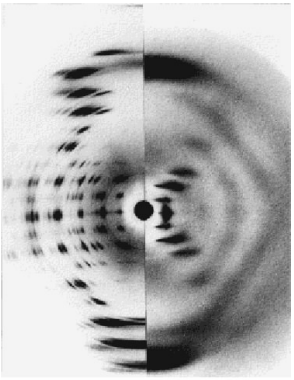
Images for DNA Structure Determination from X-Ray Patterns

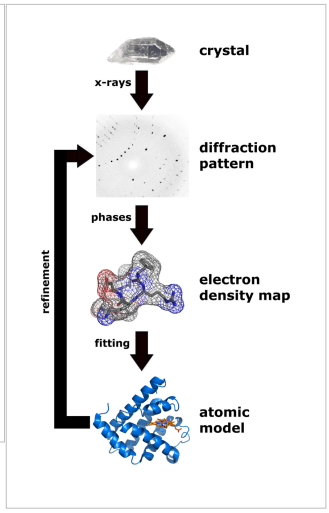
The following images illustrate both the principles and the main steps involved in generating structural information from X-ray diffraction studies of oriented DNA fibers with the help of molecular models of DNA that are combined with crystallographic and mathematical analysis of the X-ray patterns. From left to right the gallery of images shows:

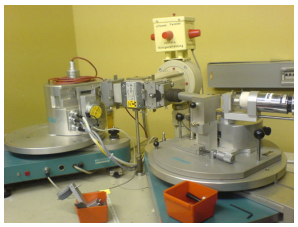
- *First row*:
- 1. Constructive X-ray interference, or diffraction, following Bragg's Law of X-ray "*reflection by the crystal planes*";
- 2. A comparison of A-DNA (crystalline) and highly hydrated B-DNA (paracrystalline) X-ray diffraction, and respectively, X-ray scattering patterns (courtesy of Dr. Herbert R. Wilson, FRS- see refs. list);
- 3. Purified DNA precipitated in a water jug;
- 4. The major steps involved in DNA structure determination by X-ray crystallography showing the important role played by molecular models of DNA structure in this iterative, structure--determination process;
- *Second row*:
- 5. Photo of a modern X-ray diffractometer employed for recording X-ray patterns of DNA with major components: X-ray source, goniometer, sample holder, X-ray detector and/or plate holder;
- 6. Illustrated animation of an X-ray goniometer;
- 7. X-ray detector at the SLAC synchrotron facility;
- 8. Neutron scattering facility at ISIS in UK;
- *Third and fourth rows*: *Molecular models of DNA structure at various scales*; figure #11 is an actual electron micrograph of a DNA fiber bundle, presumably of a single

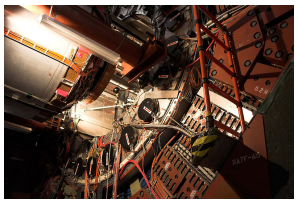
bacterial chromosome loop.

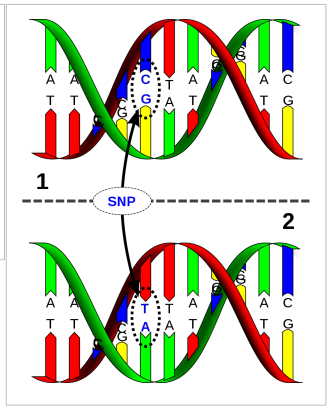


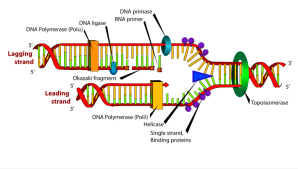


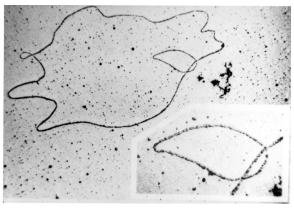


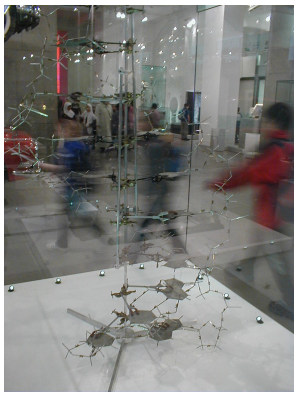


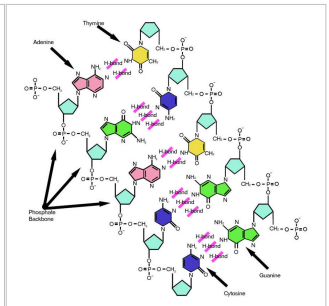


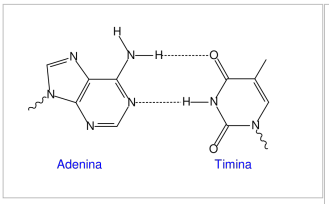


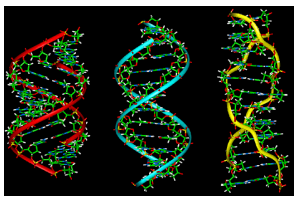


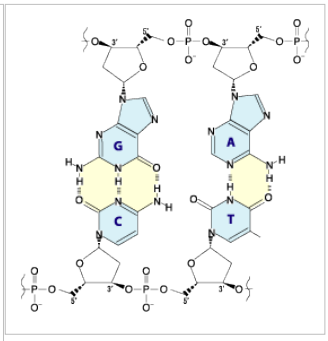


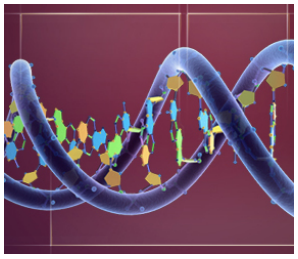


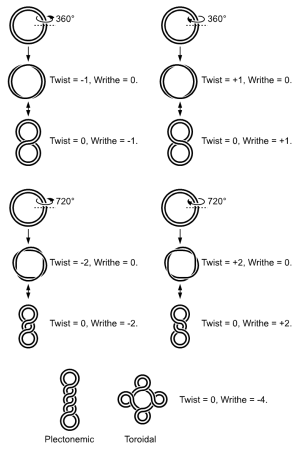


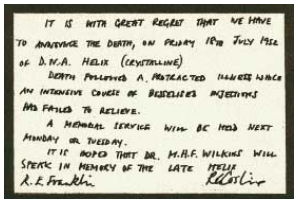






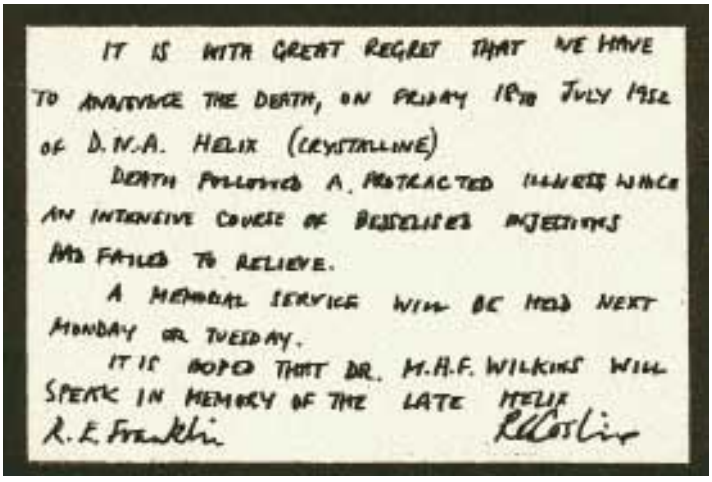






Paracrystalline lattice models of B-DNA structures

A paracrystalline lattice, or paracrystal, is a molecular or atomic lattice with significant amounts (e.g., larger than a few percent) of partial disordering of molecular arranegements. Limiting cases of the paracrystal model are nanostructures, such as glasses, liquids, etc., that may possess only local ordering and no global order. Liquid crystals also have paracrystalline rather than crystalline structures.



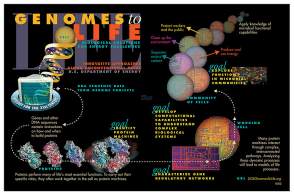
DNA Helix controversy in 1952

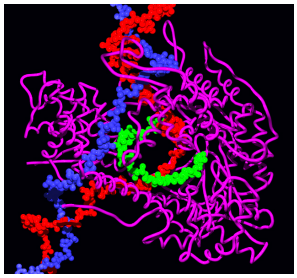
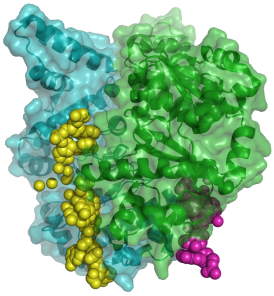
Highly hydrated B-DNA occurs naturally in living cells in such a paracrystalline state, which is a dynamic one in spite of the relatively rigid DNA double-helix stabilized by parallel hydrogen bonds between the nucleotide base-pairs in the two complementary, helical DNA chains (see figures). For simplicity most DNA molecular models ommit both water and ions dynamically bound to B-DNA, and are thus less useful for understanding the dynamic behaviors of B-DNA *in vivo*. The physical and mathematical analysis of X-ray[15] [16] and spectroscopic data for paracrystalline B-DNA is therefore much more complicated than that of crystalline, A-DNA X-ray diffraction patterns. The paracrystal model is also important for DNA technological applications such as → DNA nanotechnology. Novel techniques that combine X-ray diffraction of DNA with X-ray microscopy in hydrated living cells are now also being developed (see, for example, "Application of X-ray microscopy in the analysis of living hydrated cells" [17]).

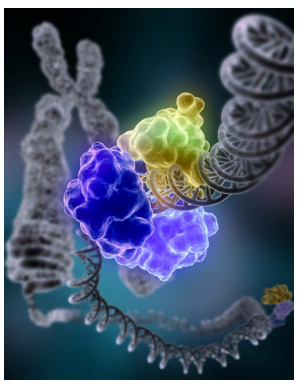
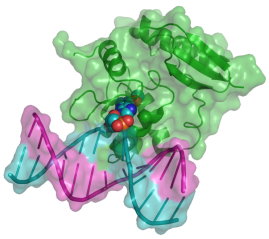
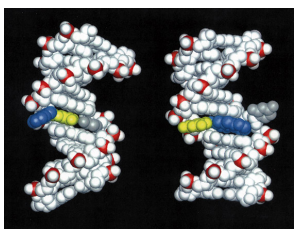
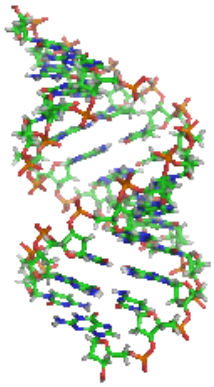
Genomic and Biotechnology Applications of DNA molecular modeling

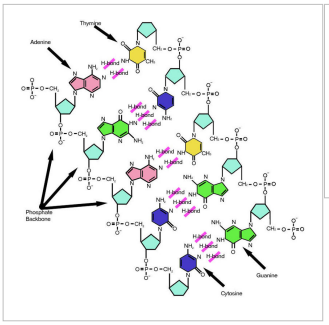
The following gallery of images illustrates various uses of DNA molecular modeling in Genomics and Biotechnology research applications from DNA repair to PCR and DNA nanostructures; each slide contains its own explanation and/or details. The first slide presents an overview of DNA applications, including DNA molecular models, with emphasis on Genomics and Biotechnology.

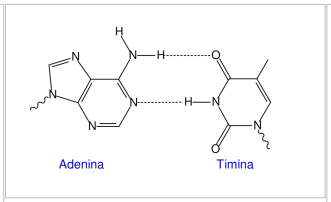
Gallery: DNA Molecular modeling applications

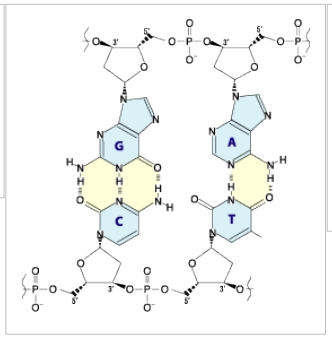


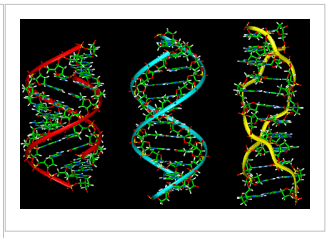



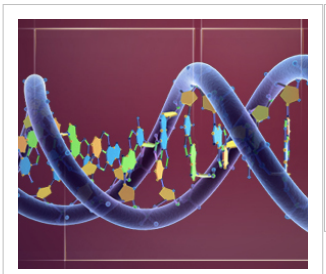





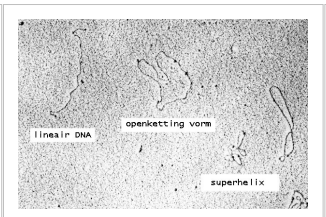

Thymine
Adenine
Phosphate Backbone
Guanine
Cytosine

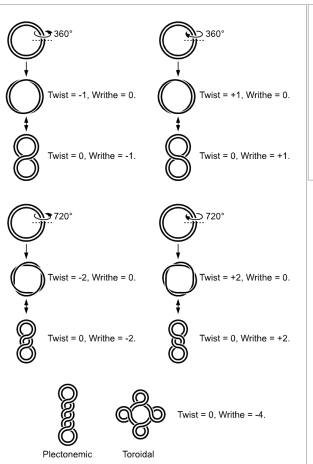

Adenina
Timina

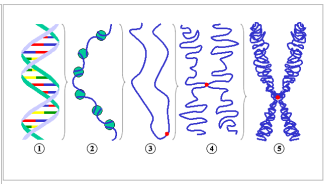

G
C
A
T

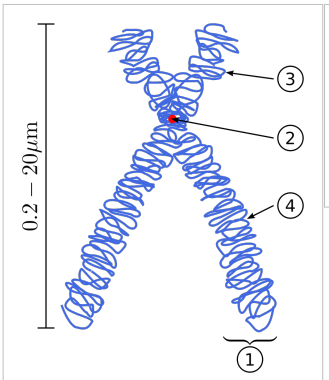


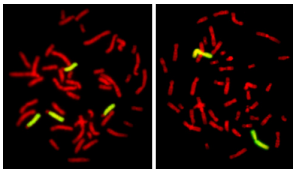


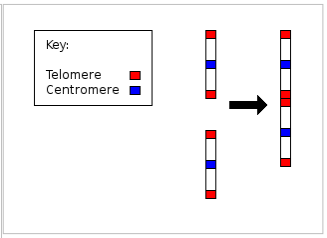

linear DNA
openkettig vorm
superhelix

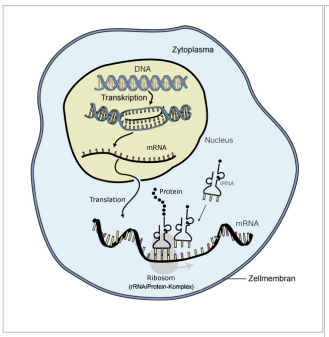

360°
Twist = -1, Writhe = 0.
Twist = 0, Writhe = -1.
360°
Twist = +1, Writhe = 0.
Twist = 0, Writhe = +1.
720°
Twist = -2, Writhe = 0.
Twist = 0, Writhe = -2.
720°
Twist = +2, Writhe = 0.
Twist = 0, Writhe = +2.
Twist = 0, Writhe = -4.
Plectonemic
Toroidal

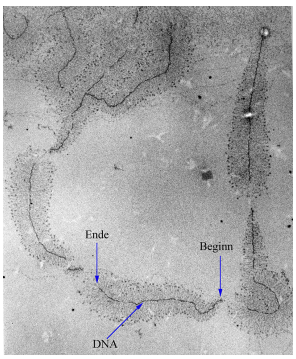

1
2
3
4
5

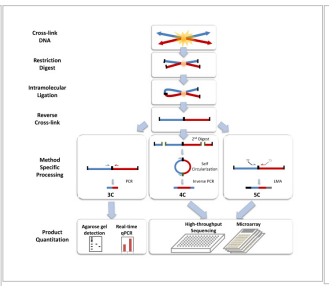

0.2 – 20µm
1
2
3
4

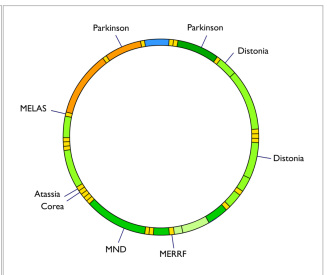


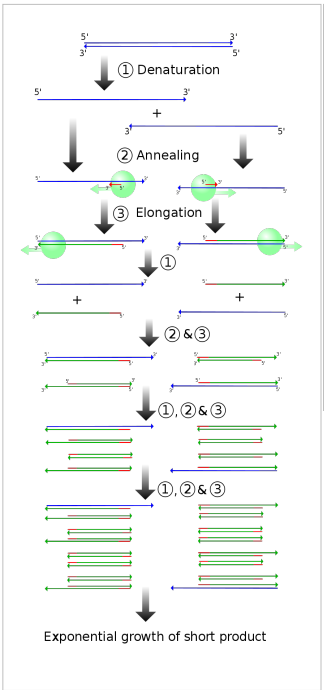

Key:
Telomere
Centromere

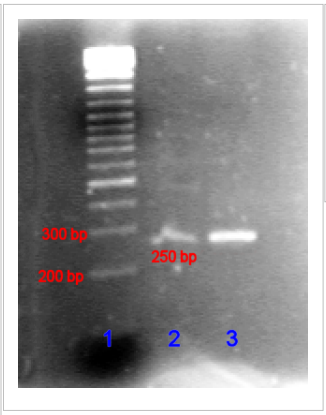

Zytoplasma
DNA
Transkription
Nucleus
mRNA
Translation
Protein
tRNA
mRNA
Ribosom
(rRNA/Protein-Komplex)
Zellmembran

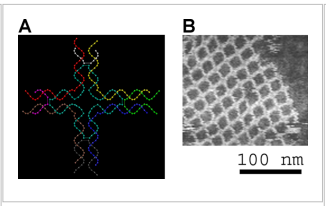

Ende
Beginn
DNA

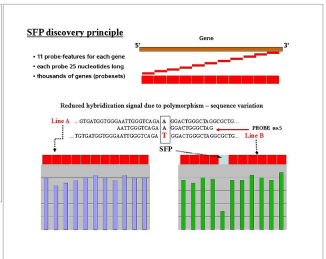

Cross-link DNA
Restriction Digest
Intramolecular Ligation
Reverse Cross-link
Method Specific Processing
3C
4C
5C
Product Quantitation

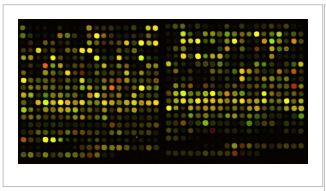

Parkinson
Parkinson
Distonia
MELAS
Distonia
Atassia
Corea
MND
MERRF

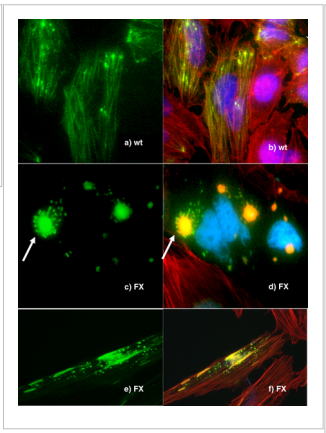


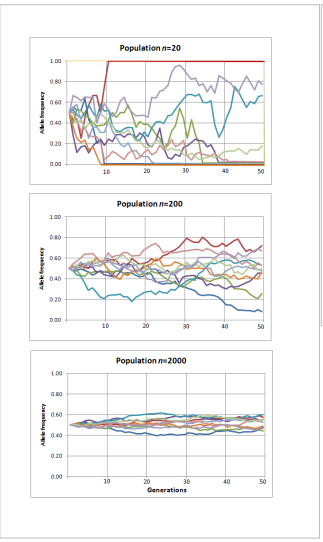












Databases for DNA molecular models and sequences

X-ray diffraction

- NDB ID: UD0017 Database [18]
- X-ray Atlas -database [19]
- PDB files of coordinates for nucleic acid structures from X-ray diffraction by NA (incl. DNA) crystals [20]
- Structure factors dowloadable files in CIF format [21]

Neutron scattering

- ISIS neutron source
- ISIS pulsed neutron source:A world centre for science with neutrons & muons at Harwell, near Oxford, UK. [22]

X-ray microscopy

- Application of X-ray microscopy in the analysis of living hydrated cells [23]

Electron microscopy

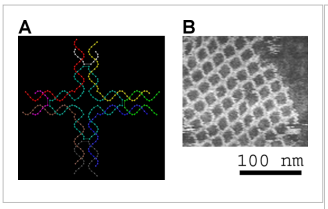
- DNA under electron microscope [24]

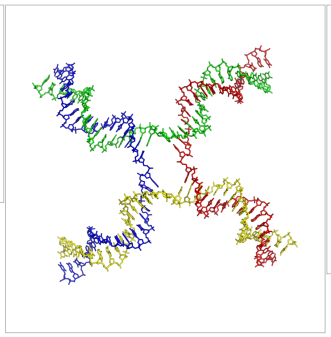
Atomic Force Microscopy (AFM)

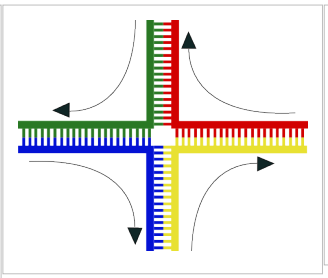
Two-dimensional DNA junction arrays have been visualized by Atomic Force Microscopy (AFM)[25] . Other imaging resources for AFM/Scanning probe microscopy(SPM) can be freely accessed at:

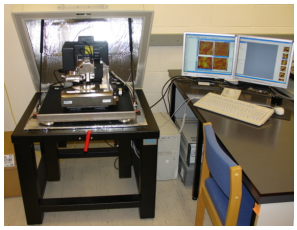
- How SPM Works [26]
- SPM Image Gallery - AFM STM SEM MFM NSOM and more. [27]

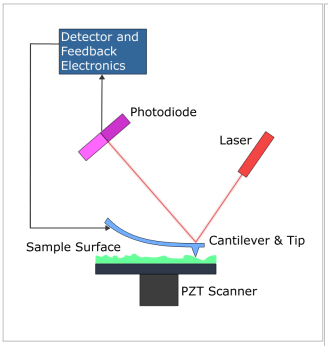
Gallery of AFM Images

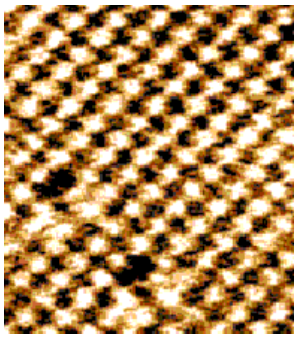


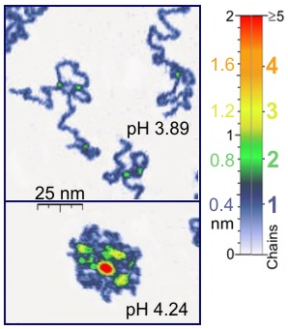


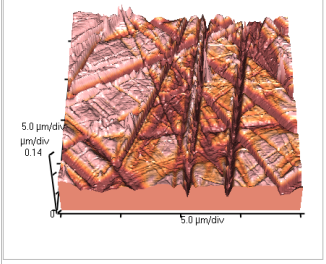




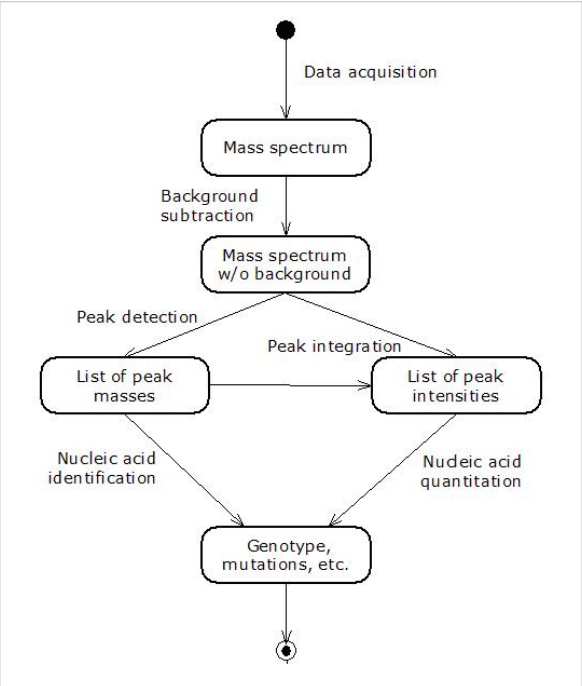








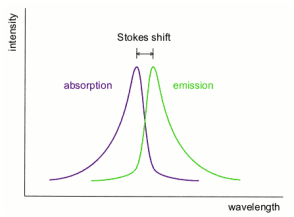
Mass spectrometry--Maldi informatics

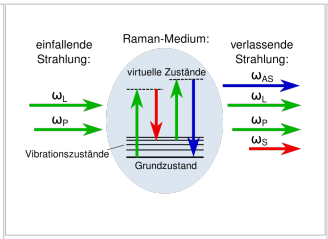


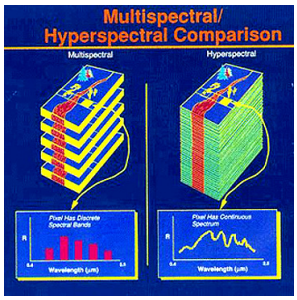
Spectroscopy

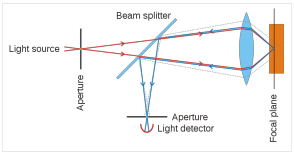
- Vibrational circular dichroism (VCD)
- FT-NMR[28] [29]
  - NMR Atlas--database [30]
  - mmcif downloadable coordinate files of nucleic acids in solution from 2D-FT NMR data [31]
  - NMR constraints files for NAs in PDB format [32]
- NMR microscopy[33]
- Microwave spectroscopy
- FT-IR
- FT-NIR[34] [35] [36]
- Spectral, Hyperspectral, and Chemical imaging)[37] [38] [39] [40] [41] [42] [43] .
- Raman spectroscopy/microscopy[44] and CARS[45] .
- Fluorescence correlation spectroscopy[46] [47] [48] [49] [50] [51] [52] [53] , Fluorescence cross-correlation spectroscopy and FRET[54] [55] [56] .
- Confocal microscopy[57]

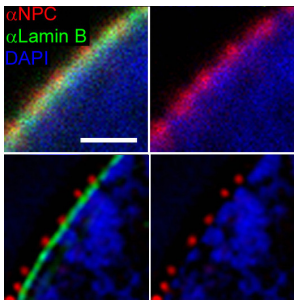
Gallery: CARS (Raman spectroscopy), Fluorescence confocal microscopy, and Hyperspectral imaging

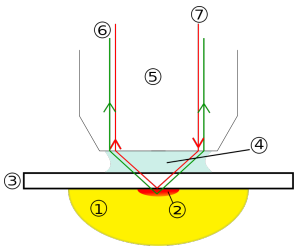


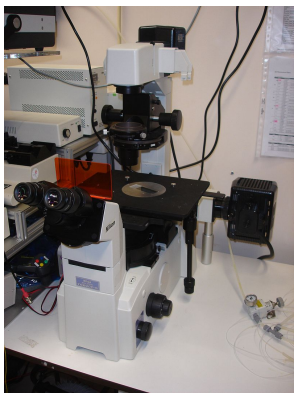


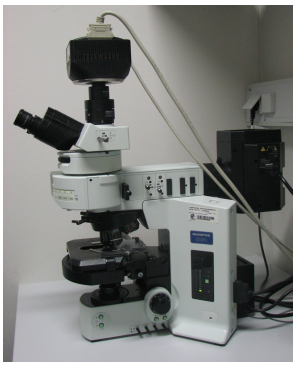


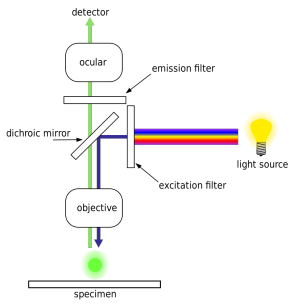


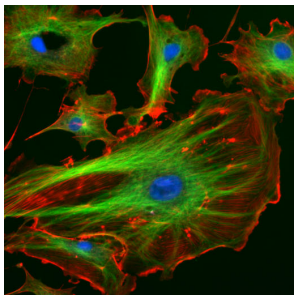


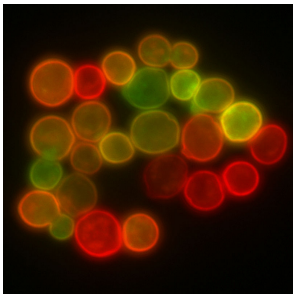


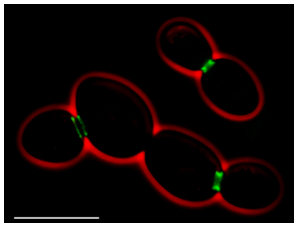


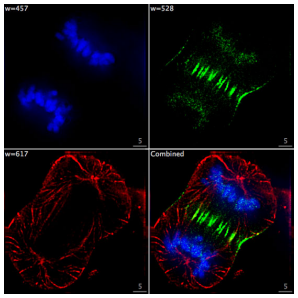


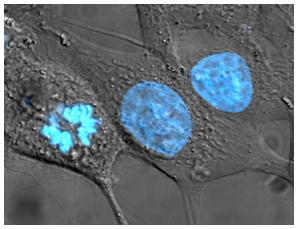


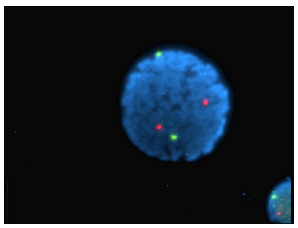


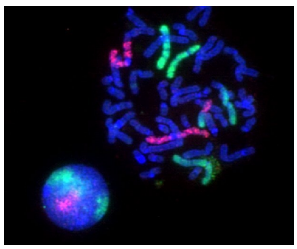


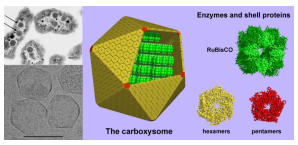












Genomic and structural databases

- CBS Genome Atlas Database [58] — contains examples of base skews.[59]
- The Z curve database of genomes — a 3-dimensional visualization and analysis tool of genomes [60][61] .
- DNA and other nucleic acids' molecular models: Coordinate files of nucleic acids molecular structure models in PDB and CIF formats [62]

Notes

[1] Franklin, R.E. and Gosling, R.G. recd.6 March 1953. Acta Cryst. (1953). 6, 673 The Structure of Sodium Thymonucleate Fibres I. The Influence of Water Content Acta Cryst. (1953). and 6, 678 The Structure of Sodium Thymonucleate Fibres II. The Cylindrically Symmetrical Patterson Function.

[2] Cochran, W., Crick, F.H.C. and Vand V. 1952. The Structure of Synthetic Polypeptides. 1. The Transform of Atoms on a Helix. Acta Cryst. 5(5):581-586.

[3] Crick, F.H.C. 1953a. The Fourier Transform of a Coiled-Coil., Acta Crystallographica 6(8-9):685-689.

[4] Watson, J.D; Crick F.H.C. 1953a. Molecular Structure of Nucleic Acids- A Structure for Deoxyribose Nucleic Acid., Nature 171(4356):737-738.

[5] Watson, J.D; Crick F.H.C. 1953b. The Structure of DNA., Cold Spring Harbor Symposia on Qunatitative Biology 18:123-131.

[6] Elson D, Chargaff E (1952). "On the deoxyribonucleic acid content of sea urchin gametes". *Experientia* **8** (4): 143-145.

[7] Chargaff E, Lipshitz R, Green C (1952). "Composition of the deoxypentose nucleic acids of four genera of sea-urchin". *J Biol Chem* **195** (1): 155-160. PMID 14938364.

[8] Chargaff E, Lipshitz R, Green C, Hodes ME (1951). "The composition of the deoxyribonucleic acid of salmon sperm". *J Biol Chem* **192** (1): 223-230. PMID 14917668.

[9] Chargaff E (1951). "Some recent studies on the composition and structure of nucleic acids". *J Cell Physiol Suppl* **38** (Suppl).

[10] Magasanik B, Vischer E, Doniger R, Elson D, Chargaff E (1950). "The separation and estimation of ribonucleotides in minute quantities". *J Biol Chem* **186** (1): 37-50. PMID 14778802.

[11] Chargaff E (1950). "Chemical specificity of nucleic acids and mechanism of their enzymatic degradation". *Experientia* **6** (6): 201-209.

[12] http://ndbserver.rutgers.edu/atlas/xray/structures/U/ud0017/ud0017.html

[13] http://www.phy.cam.ac.uk/research/bss/molbiophysics.php

[14] http://planetphysics.org/encyclopedia/TheoreticalBiophysics.html

[15] Hosemann R., Bagchi R.N., *Direct analysis of diffraction by matter*, North-Holland Publs., Amsterdam – New York, 1962.

[16] Baianu, I.C. (1978). "X-ray scattering by partially disordered membrane systems.". *Acta Cryst.*, **A34** (5): 751–753. doi: 10.1107/S0567739478001540 (http://dx.doi.org/10.1107/S0567739478001540).

[17] http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12379938

[18] http://ndbserver.rutgers.edu/atlas/xray/structures/U/ud0017/ud0017.html

[19] http://ndbserver.rutgers.edu/atlas/xray/index.html

[20] http://ndbserver.rutgers.edu/ftp/NDB/coordinates/na-biol/

[21] http://ndbserver.rutgers.edu/ftp/NDB/structure-factors/

[22] http://www.isis.rl.ac.uk/

[23] http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12379938
[24] http://www.fidelitysystems.com/Unlinked_DNA.html
[25] Mao, Chengde; Sun, Weiqiong & Seeman, Nadrian C. (16 June 1999). "Designed Two-Dimensional DNA Holliday Junction Arrays Visualized by Atomic Force Microscopy". *Journal of the American Chemical Society* **121** (23): 5437–5443. doi: 10.1021/ja9900398 (http://dx.doi.org/10.1021/ja9900398). ISSN 0002-7863 (http://worldcat.org/issn/0002-7863).
[26] http://www.parkafm.com/New_html/resources/01general.php
[27] http://www.rhk-tech.com/results/showcase.php
[28] (http://www.jonathanpmiller.com/Karplus.html)- obtaining dihedral angles from ^{3}J coupling constants
[29] (http://www.spectroscopynow.com/FCKeditor/UserFiles/File/specNOW/HTML files/General_Karplus_Calculator.htm) Another Javascript-like NMR coupling constant to dihedral
[30] http://ndbserver.rutgers.edu/atlas/nmr/index.html
[31] http://ndbserver.rutgers.edu/ftp/NDB/coordinates/na-nmr-mmcif/
[32] http://ndbserver.rutgers.edu/ftp/NDB/nmr-restraints/
[33] Lee, S. C. et al., (2001). One Micrometer Resolution NMR Microscopy. *J. Magn. Res.*, **150**: 207-213.
[34] Near Infrared Microspectroscopy, Fluorescence Microspectroscopy,Infrared Chemical Imaging and High Resolution Nuclear Magnetic Resonance Analysis of Soybean Seeds, Somatic Embryos and Single Cells., Baianu, I.C. et al. 2004., In *Oil Extraction and Analysis.*, D. Luthria, Editor pp.241-273, AOCS Press., Champaign, IL.
[35] Single Cancer Cell Detection by Near Infrared Microspectroscopy, Infrared Chemical Imaging and Fluorescence Microspectroscopy.2004.I. C. Baianu, D. Costescu, N. E. Hofmann and S. S. Korban, q-bio/0407006 (July 2004) (http://arxiv.org/abs/q-bio/0407006)
[36] Raghavachari, R., Editor. 2001. *Near-Infrared Applications in Biotechnology*, Marcel-Dekker, New York, NY.
[37] http://www.imaging.net/chemical-imaging/ Chemical imaging
[38] http://www.malvern.com/LabEng/products/sdi/bibliography/sdi_bibliography.htm E. N. Lewis, E. Lee and L. H. Kidder, Combining Imaging and Spectroscopy: Solving Problems with Near-Infrared Chemical Imaging. Microscopy Today, Volume 12, No. 6, 11/2004.
[39] D.S. Mantus and G. H. Morrison. 1991. Chemical imaging in biology and medicine using ion microscopy., *Microchimica Acta*, **104**, (1-6) January 1991, doi: 10.1007/BF01245536
[40] Near Infrared Microspectroscopy, Fluorescence Microspectroscopy,Infrared Chemical Imaging and High Resolution Nuclear Magnetic Resonance Analysis of Soybean Seeds, Somatic Embryos and Single Cells., Baianu, I.C. et al. 2004., In *Oil Extraction and Analysis.*, D. Luthria, Editor pp.241-273, AOCS Press., Champaign, IL.
[41] Single Cancer Cell Detection by Near Infrared Microspectroscopy, Infrared Chemical Imaging and Fluorescence Microspectroscopy.2004.I. C. Baianu, D. Costescu, N. E. Hofmann and S. S. Korban, q-bio/0407006 (July 2004) (http://arxiv.org/abs/q-bio/0407006)
[42] J. Dubois, G. Sando, E. N. Lewis, Near-Infrared Chemical Imaging, A Valuable Tool for the Pharmaceutical Industry, G.I.T. Laboratory Journal Europe, No.1-2, 2007.
[43] Applications of Novel Techniques to Health Foods, Medical and Agricultural Biotechnology.(June 2004).,I. C. Baianu, P. R. Lozano, V. I. Prisecaru and H. C. Lin q-bio/0406047 (http://arxiv.org/abs/q-bio/0406047)
[44] Chemical Imaging Without Dyeing (http://witec.de/en/download/Raman/ImagingMicroscopy04.pdf)
[45] C.L. Evans and X.S. Xie.2008. Coherent Anti-Stokes Raman Scattering Microscopy: Chemical Imaging for Biology and Medicine., doi:10.1146/annurev.anchem.1.031207.112754 *Annual Review of Analytical Chemistry*, **1**: 883-909.
[46] Eigen, M., Rigler, M. Sorting single molecules: application to diagnostics and evolutionary biotechnology,(1994) *Proc. Natl. Acad. Sci. USA*, 91,5740-5747.
[47] Rigler, M. Fluorescence correlations, single molecule detection and large number screening. Applications in biotechnology,(1995) J. Biotechnol., 41,177-186.
[48] Rigler R. and Widengren J. (1990). Ultrasensitive detection of single molecules by fluorescence correlation spectroscopy, *BioScience* (Ed. Klinge & Owman) p.180.
[49] Single Cancer Cell Detection by Near Infrared Microspectroscopy, Infrared Chemical Imaging and Fluorescence Microspectroscopy.2004.I. C. Baianu, D. Costescu, N. E. Hofmann, S. S. Korban and et al., q-bio/0407006 (July 2004) (http://arxiv.org/abs/q-bio/0407006)
[50] Oehlenschläger F., Schwille P. and Eigen M. (1996). Detection of HIV-1 RNA by nucleic acid sequence-based amplification combined with fluorescence correlation spectroscopy, *Proc. Natl. Acad. Sci. USA* **93**:1281.
[51] Bagatolli, L.A., and Gratton, E. (2000). Two-photon fluorescence microscopy of coexisting lipid domains in giant unilamellar vesicles of binary phospholipid mixtures. Biophys J., 78:290-305.

[52] Schwille, P., Haupts, U., Maiti, S., and Webb. W.(1999). Molecular dynamics in living cells observed by fluorescence correlation spectroscopy with one- and two-photon excitation. Biophysical Journal, 77(10):2251-2265.
[53] Near Infrared Microspectroscopy, Fluorescence Microspectroscopy,Infrared Chemical Imaging and High Resolution Nuclear Magnetic Resonance Analysis of Soybean Seeds, Somatic Embryos and Single Cells., Baianu, I.C. et al. 2004., In *Oil Extraction and Analysis.*, D. Luthria, Editor pp.241-273, AOCS Press., Champaign, IL.
[54] FRET description (http://dwb.unl.edu/Teacher/NSF/C08/C08Links/pps99.cryst.bbk.ac.uk/projects/gmocz/fret.htm)
[55] doi:10.1016/S0959-440X(00)00190-1 (http://dx.doi.org/10.1016/S0959-440X(00)00190-1)Recent advances in FRET: distance determination in protein–DNA complexes. *Current Opinion in Structural Biology* **2001**, *11(2)*, 201-207
[56] http://www.fretimaging.org/mcnamaraintro.html FRET imaging introduction
[57] Eigen, M., and Rigler, R. (1994). Sorting single molecules: Applications to diagnostics and evolutionary biotechnology, Proc. Natl. Acad. Sci. USA 91:5740.
[58] http://www.cbs.dtu.dk/services/GenomeAtlas/
[59] Hallin PF, David Ussery D (2004). "CBS Genome Atlas Database: A dynamic storage for bioinformatic results and DNA sequence data". *Bioinformatics* **20**: 3682-3686.
[60] http://tubic.tju.edu.cn/zcurve/
[61] Zhang CT, Zhang R, Ou HY (2003). "The Z curve database: a graphic representation of genome sequences". Bioinformatics 19 (5): 593-599. doi:10.1093/bioinformatics/btg041
[62] http://ndbserver.rutgers.edu/ftp/NDB/models/

References

- *Applications of Novel Techniques to Health Foods, Medical and Agricultural Biotechnology*.(June 2004) I. C. Baianu, P. R. Lozano, V. I. Prisecaru and H. C. Lin., q-bio/0406047.
- F. Bessel, *Untersuchung des Theils der planetarischen Störungen*, Berlin Abhandlungen (1824), article 14.
- Sir Lawrence Bragg, FRS. *The Crystalline State, A General survey.* London: G. Bells and Sons, Ltd., vols. 1 and 2., 1966., 2024 pages.
- Cantor, C. R. and Schimmel, P.R. *Biophysical Chemistry, Parts I and II.*, San Franscisco: W.H. Freeman and Co. 1980. 1,800 pages.
- Eigen, M., and Rigler, R. (1994). Sorting single molecules: Applications to diagnostics and evolutionary biotechnology, *Proc. Natl. Acad. Sci. USA* **91**:5740.
- Raghavachari, R., Editor. 2001. *Near-Infrared Applications in Biotechnology*, Marcel-Dekker, New York, NY.
- Rigler R. and Widengren J. (1990). Ultrasensitive detection of single molecules by fluorescence correlation spectroscopy, *BioScience* (Ed. Klinge & Owman) p.180.
- Single Cancer Cell Detection by Near Infrared Microspectroscopy, Infrared Chemical Imaging and Fluorescence Microspectroscopy.2004. I. C. Baianu, D. Costescu, N. E. Hofmann, S. S. Korban and et al., q-bio/0407006 (July 2004).
- Voet, D. and J.G. Voet. *Biochemistry*, 2nd Edn., New York, Toronto, Singapore: John Wiley & Sons, Inc., 1995, ISBN: 0-471-58651-X., 1361 pages.
- Watson, G. N. *A Treatise on the Theory of Bessel Functions.*, (1995) Cambridge University Press. ISBN 0-521-48391-3.
- Watson, James D. and Francis H.C. Crick. A structure for Deoxyribose Nucleic Acid (http://www.nature.com/nature/dna50/watsoncrick.pdf) (PDF). *Nature* 171, 737–738, 25 April 1953.
- Watson, James D. *Molecular Biology of the Gene.* New York and Amsterdam: W.A. Benjamin, Inc. 1965., 494 pages.

- Wentworth, W.E. *Physical Chemistry. A short course.*, Malden (Mass.): Blackwell Science, Inc. 2000.
- Herbert R. Wilson, FRS. *Diffraction of X-rays by proteins, Nucleic Acids and Viruses.*, London: Edward Arnold (Publishers) Ltd. 1966.
- Kurt Wuthrich. *NMR of Proteins and Nucleic Acids.*, New York, Brisbane,Chicester, Toronto, Singapore: J. Wiley & Sons. 1986., 292 pages.
- Robinson, Bruche H.; Seeman, Nadrian C. (August 1987). "The Design of a Biochip: A Self-Assembling Molecular-Scale Memory Device". *Protein Engineering* **1** (4): 295–300. ISSN 0269-2139 (http://worldcat.org/issn/0269-2139). Link (http://peds.oxfordjournals.org/cgi/content/abstract/1/4/295)
- Rothemund, Paul W. K.; Ekani-Nkodo, Axel; Papadakis, Nick; Kumar, Ashish; Fygenson, Deborah Kuchnir & Winfree, Erik (22 December 2004). "Design and Characterization of Programmable DNA Nanotubes". *Journal of the American Chemical Society* **126** (50): 16344–16352. doi: 10.1021/ja044319l (http://dx.doi.org/10.1021/ja044319l). ISSN 0002-7863 (http://worldcat.org/issn/0002-7863).
- Keren, K.; Kinneret Keren, Rotem S. Berman, Evgeny Buchstab, Uri Sivan, Erez Braun (November 2003). " DNA-Templated Carbon Nanotube Field-Effect Transistor (http://www.sciencemag.org/cgi/content/abstract/sci;302/5649/1380)". *Science* **302** (6549): 1380–1382. doi: 10.1126/science.1091022 (http://dx.doi.org/10.1126/science.1091022). ISSN 1095-9203 (http://worldcat.org/issn/1095-9203). http://www.sciencemag.org/cgi/content/abstract/sci;302/5649/1380.
- Zheng, Jiwen; Constantinou, Pamela E.; Micheel, Christine; Alivisatos, A. Paul; Kiehl, Richard A. & Seeman Nadrian C. (2006). "2D Nanoparticle Arrays Show the Organizational Power of Robust DNA Motifs". *Nano Letters* **6**: 1502–1504. doi: 10.1021/nl060994c (http://dx.doi.org/10.1021/nl060994c). ISSN 1530-6984 (http://worldcat.org/issn/1530-6984).
- Cohen, Justin D.; Sadowski, John P.; Dervan, Peter B. (2007). "Addressing Single Molecules on DNA Nanostructures". *Angewandte Chemie* **46** (42): 7956–7959. doi: 10.1002/anie.200702767 (http://dx.doi.org/10.1002/anie.200702767). ISSN 0570-0833 (http://worldcat.org/issn/0570-0833).
- Mao, Chengde; Sun, Weiqiong & Seeman, Nadrian C. (16 June 1999). "Designed Two-Dimensional DNA Holliday Junction Arrays Visualized by Atomic Force Microscopy". *Journal of the American Chemical Society* **121** (23): 5437–5443. doi: 10.1021/ja9900398 (http://dx.doi.org/10.1021/ja9900398). ISSN 0002-7863 (http://worldcat.org/issn/0002-7863).
- Constantinou, Pamela E.; Wang, Tong; Kopatsch, Jens; Israel, Lisa B.; Zhang, Xiaoping; Ding, Baoquan; Sherman, William B.; Wang, Xing; Zheng, Jianping; Sha, Ruojie & Seeman, Nadrian C. (2006). "Double cohesion in structural DNA nanotechnology". *Organic and Biomolecular Chemistry* **4**: 3414–3419. doi: 10.1039/b605212f (http://dx.doi.org/10.1039/b605212f).

See also

- → DNA
- Molecular graphics
- → DNA structure
- → DNA Dynamics
- X-ray scattering
- Neutron scattering
- Crystallography
- Crystal lattices
- Paracrystalline lattices/Paracrystals
- → 2D-FT NMRI and Spectroscopy
- NMR Spectroscopy
- Microwave spectroscopy
- Two-dimensional IR spectroscopy
- Spectral imaging
- Hyperspectral imaging
- Chemical imaging
- NMR microscopy
- VCD or Vibrational circular dichroism
- FRET and FCS- Fluorescence correlation spectroscopy
- Fluorescence cross-correlation spectroscopy (FCCS)
- Molecular structure
- Molecular geometry
- Molecular topology
- DNA topology
- Sirius visualization software
- Nanostructure
- → DNA nanotechnology
- Imaging
- Atomic force microscopy
- X-ray microscopy
- Liquid crystal
- Glasses
- QMC@Home
- Sir Lawrence Bragg, FRS
- Sir John Randall
- James Watson
- Francis Crick
- Maurice Wilkins
- Herbert Wilson, FRS
- Alex Stokes

External links

- DNA the Double Helix Game (http://nobelprize.org/educational_games/medicine/dna_double_helix/) From the official Nobel Prize web site
- MDDNA: Structural Bioinformatics of DNA (http://humphry.chem.wesleyan.edu:8080/MDDNA/)
- Double Helix 1953–2003 (http://www.ncbe.reading.ac.uk/DNA50/) National Centre for Biotechnology Education
- DNA under electron microscope (http://www.fidelitysystems.com/Unlinked_DNA.html)
- Ascalaph DNA (http://www.agilemolecule.com/Ascalaph/Ascalaph_DNA.html) — Commercial software for DNA modeling
- DNAlive: a web interface to compute DNA physical properties (http://mmb.pcb.ub.es/DNAlive). Also allows cross-linking of the results with the UCSC Genome browser and DNA dynamics.
- DiProDB: Dinucleotide Property Database (http://diprodb.fli-leibniz.de). The database is designed to collect and analyse thermodynamic, structural and other dinucleotide properties.
- Further details of mathematical and molecular analysis of DNA structure based on X-ray data (http://planetphysics.org/encyclopedia/BesselFunctionsApplicationsToDiffractionByHelicalStructures.html)
- Bessel functions corresponding to Fourier transforms of atomic or molecular helices. (http://planetphysics.org/?op=getobj&from=objects&name=BesselFunctionsAndTheirApplicationsToDiffractionByHelicalStructures)
- Application of X-ray microscopy in analysis of living hydrated cells (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12379938)
- Characterization in nanotechnology some pdfs (http://nanocharacterization.sitesled.com/)
- overview of STM/AFM/SNOM principles with educative videos (http://www.ntmdt.ru/SPM-Techniques/Principles/)
- SPM Image Gallery - AFM STM SEM MFM NSOM and More (http://www.rhk-tech.com/results/showcase.php)
- How SPM Works (http://www.parkafm.com/New_html/resources/01general.php)
- U.S. National DNA Day (http://www.genome.gov/10506367) — watch videos and participate in real-time discusssions with scientists.
- The Secret Life of DNA - DNA Music compositions (http://www.tjmitchell.com/stuart/dna.html)

DNA Dynamics and Spectroscopy

DNA Dynamics

DNA Molecular dynamics modeling involves simulations of → DNA molecular geometry and topology changes with time as a result of both intra- and inter- molecular interactions of DNA. Whereas molecular models of Deoxyribonucleic acid (→ DNA) molecules such as closely packed spheres (CPK models) made of plastic or metal wires for 'skeletal models' are useful representations of static DNA structures, their usefulness is very limited for representing complex DNA dynamics. Computer molecular modeling allows both animations and molecular dynamics simulations that are very important for understanding how DNA functions *in vivo*.

An old standing dynamic problem is how DNA "self-replication" takes place in living cells that should involve transient uncoiling of supercoiled DNA fibers. Although DNA consists of relatively rigid, very large elongated biopolymer molecules called "fibers" or chains its molecular structure *in vivo* undergoes dynamic configuration changes that involve dynamically attached water molecules, ions or proteins/enzymes. Supercoiling, packing with histones in chromosome structures, and other such supramolecular aspects also involve *in vivo* DNA topology which is even more complex than DNA molecular geometry, thus turning molecular modeling of DNA dynamics into a series of challenging problems for biophysical chemists, molecular biologists and biotechnologists. Thus, DNA exists in multiple stable geometries (called conformational isomerism) and has a rather large number of configurational, quantum states which are close to each other in energy on the potential energy surface of the DNA molecule.

Such varying molecular geometries can also be computed, at least in principle, by employing *ab initio* quantum chemistry methods that can attain high accuracy for small molecules, although claims that acceptable accuracy can be also achieved for polynuclelotides, as well as DNA conformations, were recently made on the basis of VCD spectral data. Such quantum geometries define an important class of *ab initio* molecular models of DNA whose exploration has barely started especially in connection with results obtained by VCD in solutions. More detailed comparisons with such *ab initio* quantum computations are in principle obtainable through 2D-FT NMR spectroscopy and relaxation studies of polynucleotide solutions or specifically labeled DNA, as for example with deuterium labels.

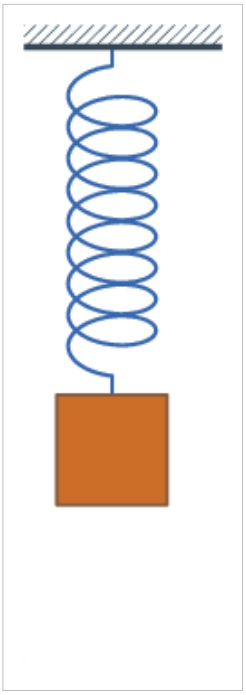
Importance of DNA molecular structure and dynamics modeling for Genomics and beyond

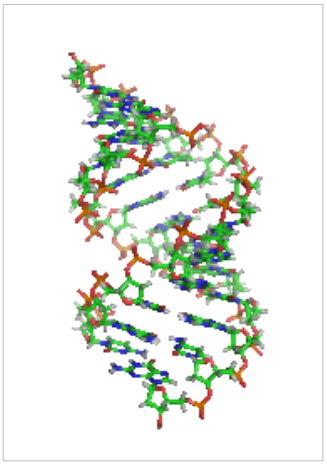
From the very early stages of structural studies of DNA by X-ray diffraction and biochemical means, molecular models such as the Watson-Crick double-helix model were successfully employed to solve the 'puzzle' of DNA structure, and also find how the latter relates to its key functions in living cells. The first high quality X-ray diffraction patterns of A-DNA were reported by Rosalind Franklin and Raymond Gosling in 1953[1] . The first reports of a double-helix molecular model of B-DNA structure were made by Watson and

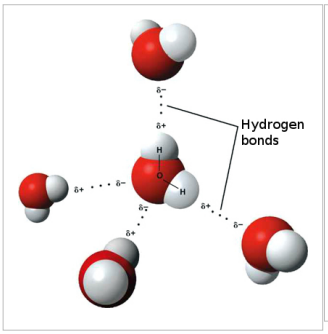
Crick in 1953[2] [3] . Then Maurice F. Wilkins, A. Stokes and H.R. Wilson, reported the first X-ray patterns of *in vivo* B-DNA in partially oriented salmon sperm heads [4] . The development of the first correct double-helix molecular model of DNA by Crick and Watson may not have been possible without the biochemical evidence for the nucleotide base-pairing ([A---T]; [C---G]), or Chargaff's rules[5] [6] [7] [8] [9] [10] . Although such initial studies of DNA structures with the help of molecular models were essentially static, their consequences for explaining the *in vivo* functions of DNA were significant in the areas of protein biosynthesis and the quasi-universality of the genetic code. Epigenetic transformation studies of DNA *in vivo* were however much slower to develop in spite of their importance for embryology, morphogenesis and cancer research. Such chemical dynamics and biochemical reactions of DNA are much more complex than the molecular dynamics of DNA physical interactions with water, ions and proteins/enzymes in living cells.

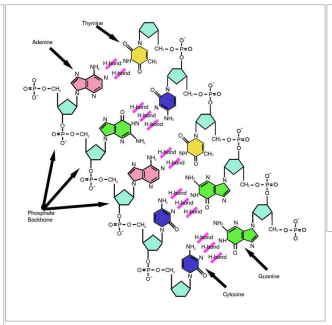
Animated DNA molecular models and hydrogen-bonding

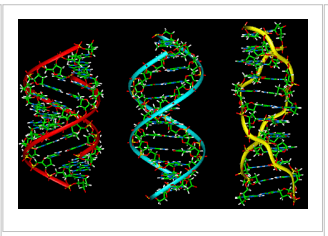
Animated molecular models allow one to visually explore the three-dimensional (3D) structure of DNA. The first DNA model is a space-filling, or CPK, model of the DNA double-helix whereas the third is an animated wire, or skeletal type, molecular model of DNA. The last two DNA molecular models in this series depict quadruplex DNA [11] that may be involved in certain cancers[12] [13] . The first CPK model in the second row is a molecular model of hydrogen bonds between water molecules in ice that are broadly similar to those found in DNA; the hydrogen bonding dynamics and proton exchange is however very different by many orders of magnitude between the two systems of fully hydrated DNA and water molecules in ice. Thus, the DNA dynamics is complex, involving nanosecond and several tens of picosecond time scales, whereas that of liquid ice is on the picosecond time scale, and that of proton exchange in ice is on the millisecond time scale; the proton exchange rates in DNA and attached proteins may vary from picosecond to nanosecond, minutes or years, depending on the exact locations of the exchanged protons in the large biopolymers. The simple harmonic oscillator 'vibration' in the third, animated image of the next gallery is only an oversimplified dynamic representation of the longitudinal vibrations of the DNA intertwined helices which were found to be anharmonic rather than harmonic as often assumed in quantum dynamic simulations of DNA.

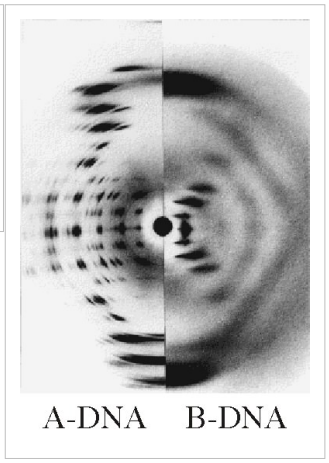


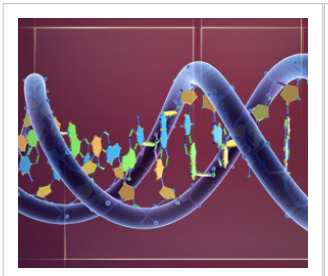


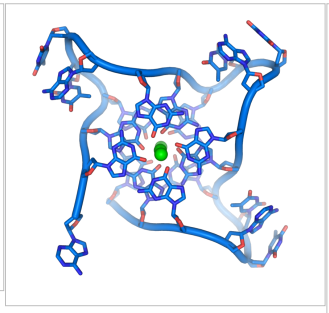

Hydrogen
bonds

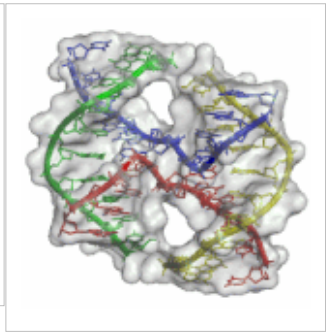





A-DNA B-DNA





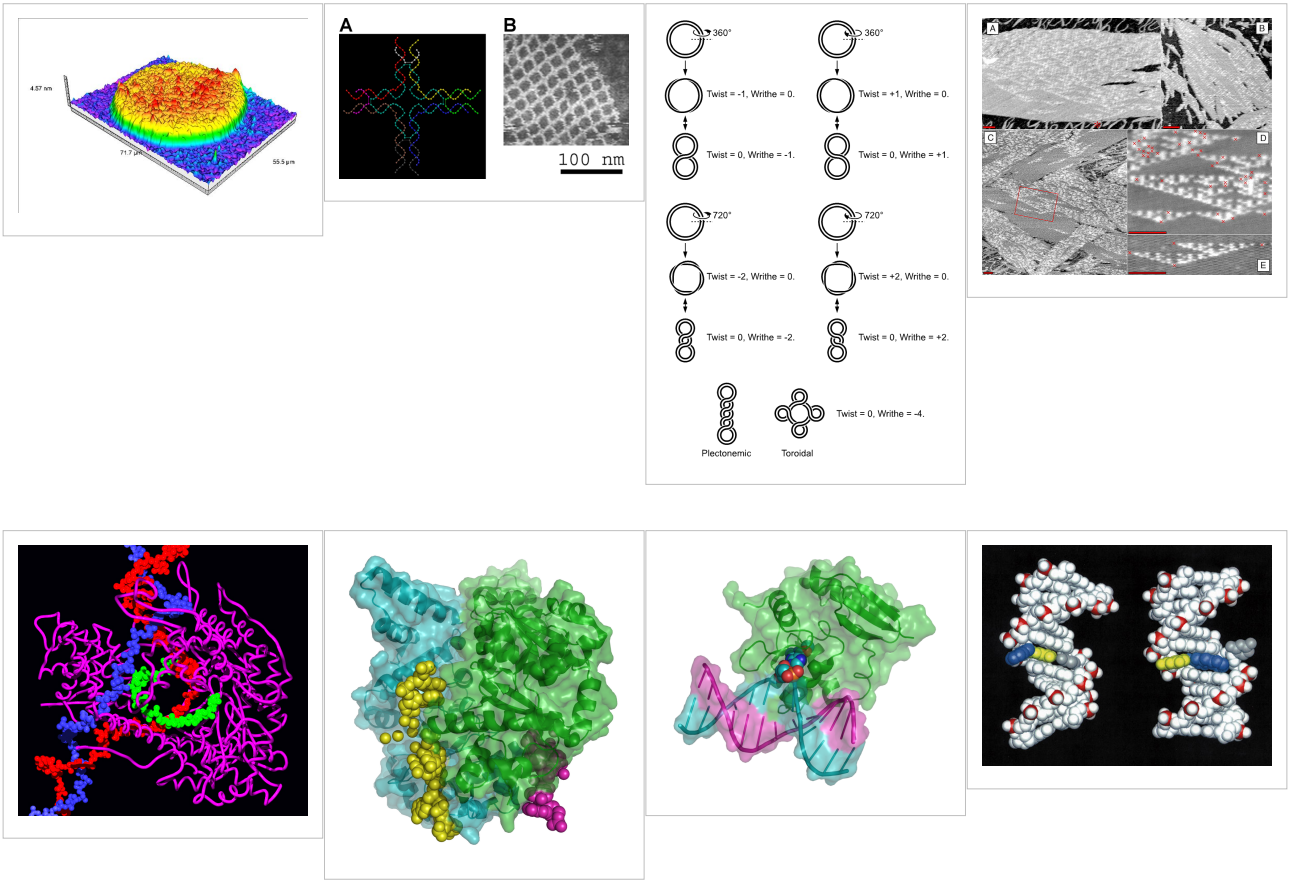


Human Genomics and Biotechnology Applications of DNA Molecular Modeling

The following two galleries of images illustrate various uses of DNA molecular modeling in Genomics and Biotechnology research applications from DNA repair to PCR and DNA nanostructures; each slide contains its own explanation and/or details. The first slide presents an overview of DNA applications, including DNA molecular models, with emphasis on Genomics and Biotechnology.

Applications of DNA molecular dynamics computations

- *First row* images present a DNA biochip and DNA nanostructures designed for DNA computing and other dynamic applications of DNA nanotechnology; last image in this row is of DNA arrays that display a representation of the Sierpinski gasket on their surfaces.
- *Second row*: the first two images show computer molecular models of RNA polymerase, followed by that of an E. coli, bacterial DNA primase template suggesting very complex dynamics at the interfaces between the enzymes and the DNA template; the fourth image illustrates in a computed molecular model the mutagenic, chemical interaction of a potent carcinogen molecule with DNA, and the last image shows the different interactions of specific fluorescence labels with DNA in human and orangoutan chromosomes.



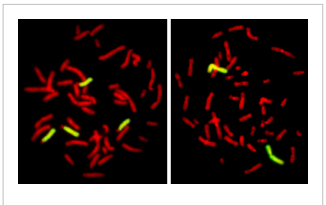
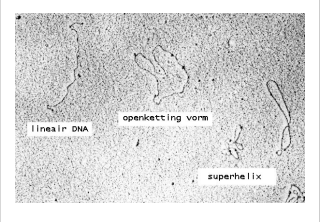
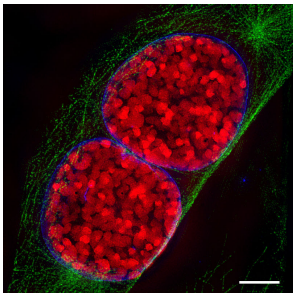
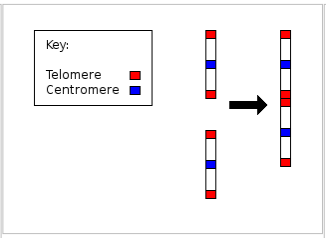


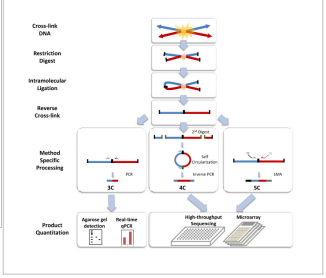
Image Gallery: *DNA Applications and Technologies at various scales in Biotechnology and Genomics research*

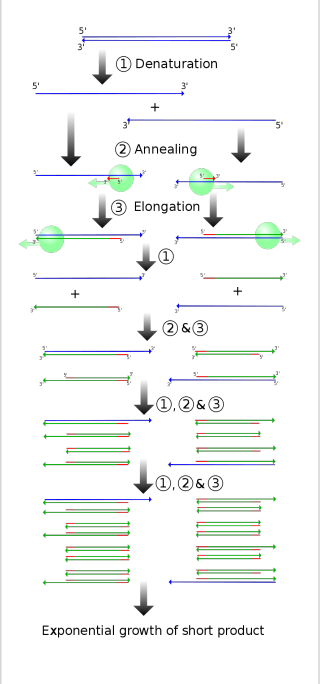
The first figure is an actual electron micrograph of a DNA fiber bundle, presumably of a single plasmid, bacterial DNA loop.

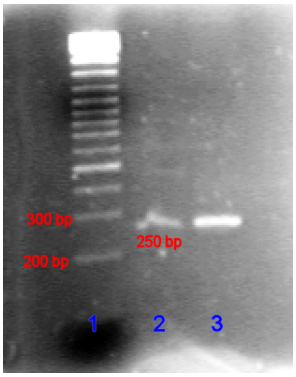


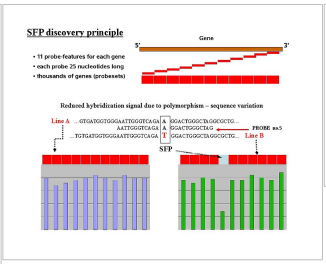


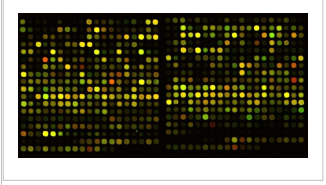


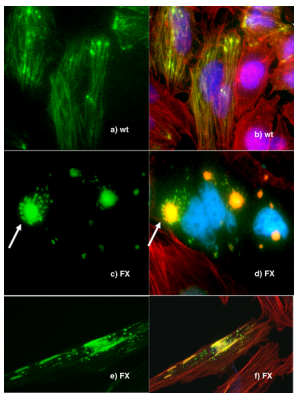


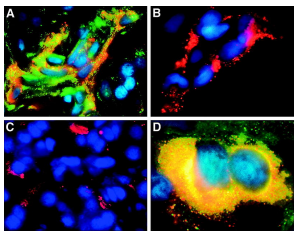


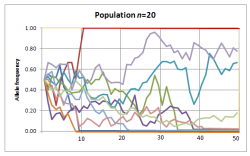


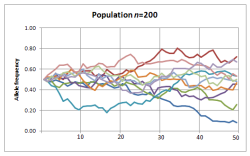


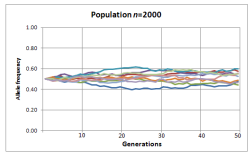


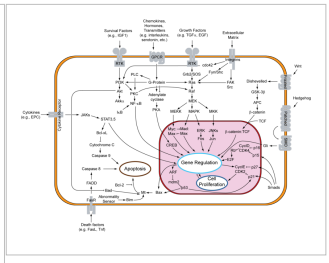


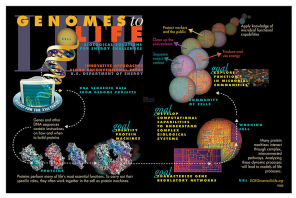










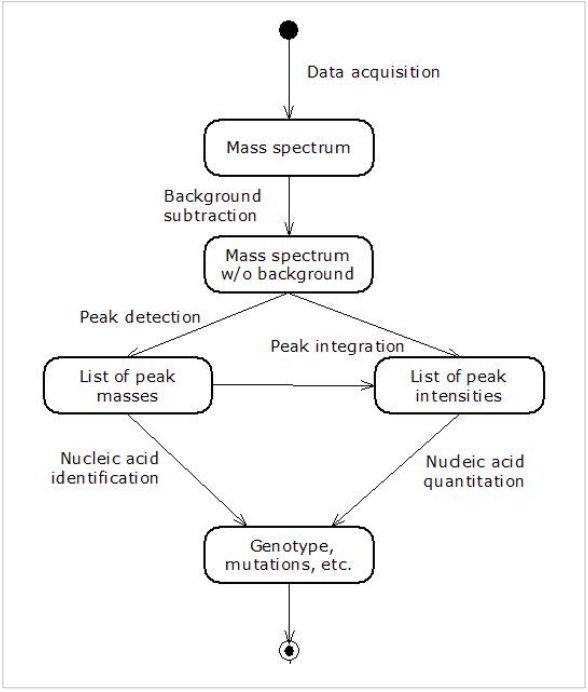


Databases for Genomics, DNA Dynamics and Sequencing

Genomic and structural databases

- CBS Genome Atlas Database [14] — contains examples of base skews.[15]
- The Z curve database of genomes — a 3-dimensional visualization and analysis tool of genomes [16][17] .
- DNA and other nucleic acids' molecular models: Coordinate files of nucleic acids molecular structure models in PDB and CIF formats [18]

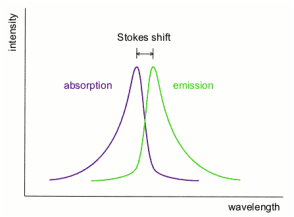
Mass spectrometry--Maldi informatics

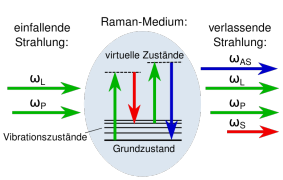


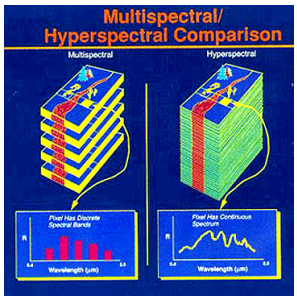
DNA Dynamics Data from Spectroscopy

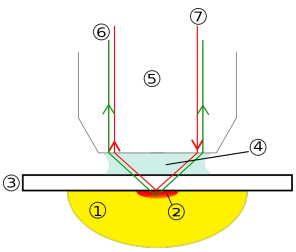
- FT-NMR[19] [20]
  - NMR Atlas--database [21]
  - mmcif downloadable coordinate files of nucleic acids in solution from 2D-FT NMR data [22]
  - NMR constraints files for NAs in PDB format [23]
- NMR microscopy[24]
- Vibrational circular dichroism (VCD)
- Microwave spectroscopy
- FT-IR
- FT-NIR[25] [26] [27]
- Spectral, Hyperspectral, and Chemical imaging)[28] [29] [30] [31] [32] [33] [34] .
- Raman spectroscopy/microscopy[35] and CARS[36] .
- Fluorescence correlation spectroscopy[37] [38] [39] [40] [41] [42] [43] [44] , Fluorescence cross-correlation spectroscopy and FRET[45] [46] [47] .
- Confocal microscopy[48]

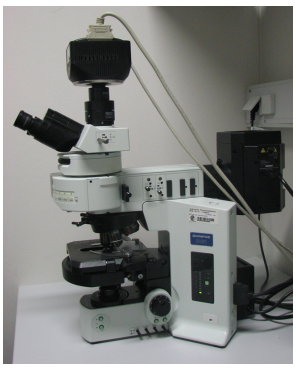
Gallery: CARS (Raman spectroscopy), Fluorescence confocal microscopy, and Hyperspectral imaging

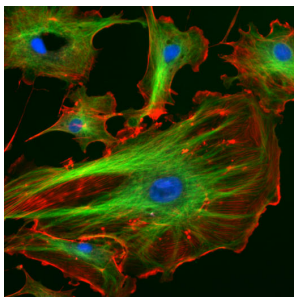


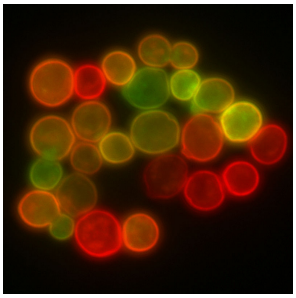


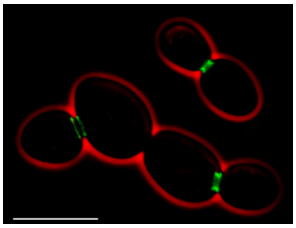


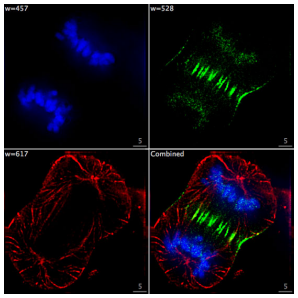


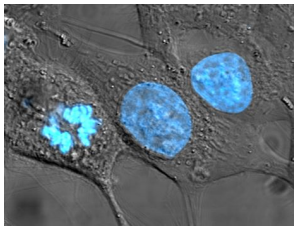


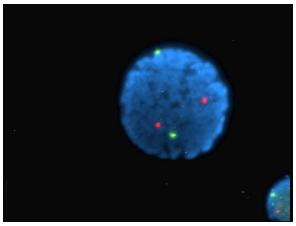


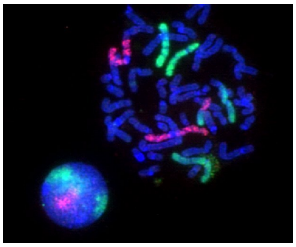


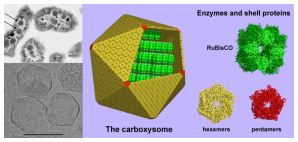












X-ray microscopy

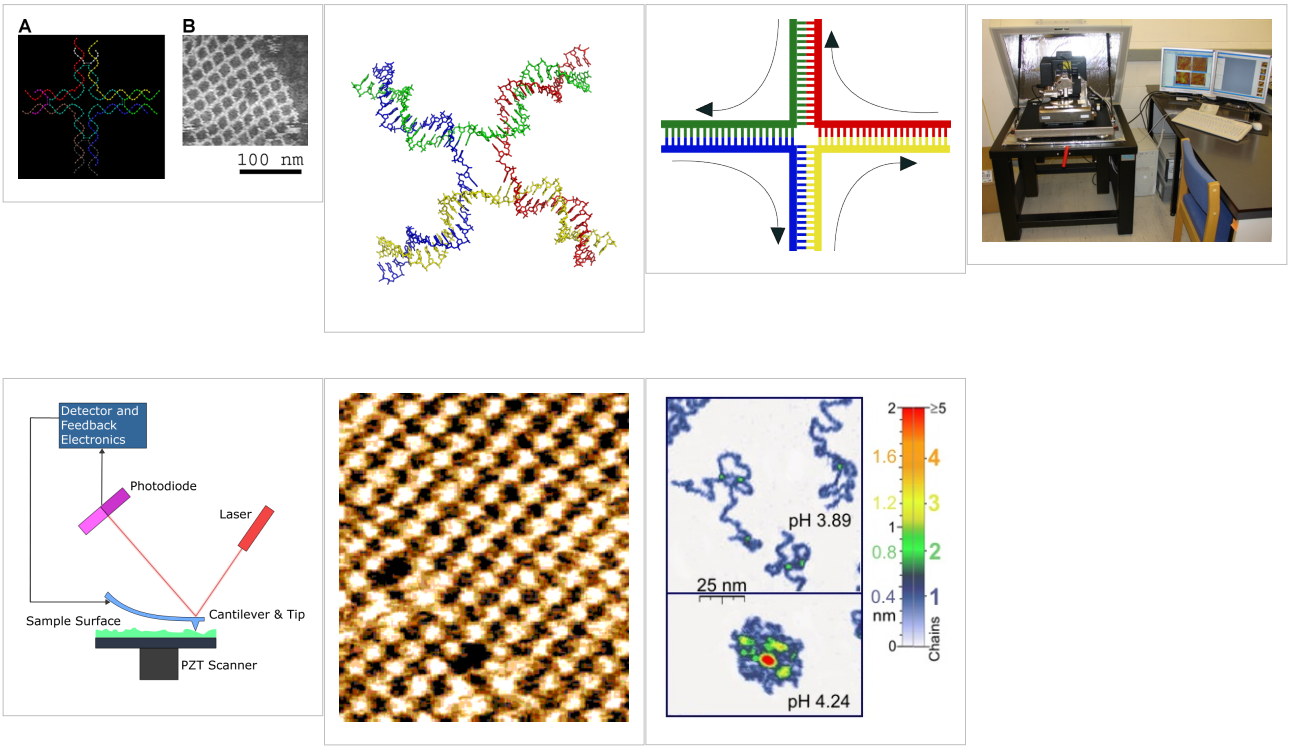
- Application of X-ray microscopy in the analysis of living hydrated cells [49]

Atomic Force Microscopy (AFM)

Two-dimensional DNA junction arrays have been visualized by Atomic Force Microscopy (AFM)[50] . Other imaging resources for AFM/Scanning probe microscopy(SPM) can be freely accessed at:

- How SPM Works [51]
- SPM Image Gallery - AFM STM SEM MFM NSOM and more. [52]

Gallery of AFM Images of DNA Nanostructures



Notes

[1] Franklin, R.E. and Gosling, R.G. recd.6 March 1953. Acta Cryst. (1953). 6, 673 The Structure of Sodium Thymonucleate Fibres I. The Influence of Water Content Acta Cryst. (1953). and 6, 678 The Structure of Sodium Thymonucleate Fibres II. The Cylindrically Symmetrical Patterson Function.

[2] Watson, J.D; Crick F.H.C. 1953a. Molecular Structure of Nucleic Acids- A Structure for Deoxyribose Nucleic Acid., Nature 171(4356):737-738.

[3] Watson, J.D; Crick F.H.C. 1953b. The Structure of DNA., Cold Spring Harbor Symposia on Quantitative Biology 18:123-131.

[4] Wilkins M.H.F., A.R. Stokes A.R. & Wilson, H.R. (1953). " Molecular Structure of Deoxypentose Nucleic Acids (http://www.nature.com/nature/dna50/wilkins.pdf)" (PDF). *Nature* **171**: 738–740. doi: 10.1038/171738a0 (http://dx.doi.org/10.1038/171738a0). PMID 13054693. .

[5] Elson D, Chargaff E (1952). "On the deoxyribonucleic acid content of sea urchin gametes". *Experientia* **8** (4): 143-145.

[6] Chargaff E, Lipshitz R, Green C (1952). "Composition of the deoxypentose nucleic acids of four genera of sea-urchin". *J Biol Chem* **195** (1): 155-160. PMID 14938364.

[7] Chargaff E, Lipshitz R, Green C, Hodes ME (1951). "The composition of the deoxyribonucleic acid of salmon sperm". *J Biol Chem* **192** (1): 223-230. PMID 14917668.

[8] Chargaff E (1951). "Some recent studies on the composition and structure of nucleic acids". *J Cell Physiol Suppl* **38** (Suppl).
[9] Magasanik B, Vischer E, Doniger R, Elson D, Chargaff E (1950). "The separation and estimation of ribonucleotides in minute quantities". *J Biol Chem* **186** (1): 37-50. PMID 14778802.
[10] Chargaff E (1950). "Chemical specificity of nucleic acids and mechanism of their enzymatic degradation". *Experientia* **6** (6): 201-209.
[11] http://ndbserver.rutgers.edu/atlas/xray/structures/U/ud0017/ud0017.html
[12] http://www.phy.cam.ac.uk/research/bss/molbiophysics.php
[13] http://planetphysics.org/encyclopedia/TheoreticalBiophysics.html
[14] http://www.cbs.dtu.dk/services/GenomeAtlas/
[15] Hallin PF, David Ussery D (2004). "CBS Genome Atlas Database: A dynamic storage for bioinformatic results and DNA sequence data". *Bioinformatics* **20**: 3682-3686.
[16] http://tubic.tju.edu.cn/zcurve/
[17] Zhang CT, Zhang R, Ou HY (2003). "The Z curve database: a graphic representation of genome sequences". Bioinformatics 19 (5): 593-599. doi:10.1093/bioinformatics/btg041
[18] http://ndbserver.rutgers.edu/ftp/NDB/models/
[19] (http://www.jonathanpmiller.com/Karplus.html)- obtaining dihedral angles from ^{3}J coupling constants
[20] (http://www.spectroscopynow.com/FCKeditor/UserFiles/File/specNOW/HTML files/General_Karplus_Calculator.htm) Another Javascript-like NMR coupling constant to dihedral
[21] http://ndbserver.rutgers.edu/atlas/nmr/index.html
[22] http://ndbserver.rutgers.edu/ftp/NDB/coordinates/na-nmr-mmcif/
[23] http://ndbserver.rutgers.edu/ftp/NDB/nmr-restraints/
[24] Lee, S. C. et al., (2001). One Micrometer Resolution NMR Microscopy. *J. Magn. Res.*, **150**: 207-213.
[25] Near Infrared Microspectroscopy, Fluorescence Microspectroscopy,Infrared Chemical Imaging and High Resolution Nuclear Magnetic Resonance Analysis of Soybean Seeds, Somatic Embryos and Single Cells., Baianu, I.C. et al. 2004., In *Oil Extraction and Analysis.*, D. Luthria, Editor pp.241-273, AOCS Press., Champaign, IL.
[26] Single Cancer Cell Detection by Near Infrared Microspectroscopy, Infrared Chemical Imaging and Fluorescence Microspectroscopy.2004.I. C. Baianu, D. Costescu, N. E. Hofmann and S. S. Korban, q-bio/0407006 (July 2004) (http://arxiv.org/abs/q-bio/0407006)
[27] Raghavachari, R., Editor. 2001. *Near-Infrared Applications in Biotechnology*, Marcel-Dekker, New York, NY.
[28] http://www.imaging.net/chemical-imaging/ Chemical imaging
[29] http://www.malvern.com/LabEng/products/sdi/bibliography/sdi_bibliography.htm E. N. Lewis, E. Lee and L. H. Kidder, Combining Imaging and Spectroscopy: Solving Problems with Near-Infrared Chemical Imaging. Microscopy Today, Volume 12, No. 6, 11/2004.
[30] D.S. Mantus and G. H. Morrison. 1991. Chemical imaging in biology and medicine using ion microscopy., *Microchimica Acta*, **104**, (1-6) January 1991, doi: 10.1007/BF01245536
[31] Near Infrared Microspectroscopy, Fluorescence Microspectroscopy,Infrared Chemical Imaging and High Resolution Nuclear Magnetic Resonance Analysis of Soybean Seeds, Somatic Embryos and Single Cells., Baianu, I.C. et al. 2004., In *Oil Extraction and Analysis.*, D. Luthria, Editor pp.241-273, AOCS Press., Champaign, IL.
[32] Single Cancer Cell Detection by Near Infrared Microspectroscopy, Infrared Chemical Imaging and Fluorescence Microspectroscopy.2004.I. C. Baianu, D. Costescu, N. E. Hofmann and S. S. Korban, q-bio/0407006 (July 2004) (http://arxiv.org/abs/q-bio/0407006)
[33] J. Dubois, G. Sando, E. N. Lewis, Near-Infrared Chemical Imaging, A Valuable Tool for the Pharmaceutical Industry, G.I.T. Laboratory Journal Europe, No.1-2, 2007.
[34] Applications of Novel Techniques to Health Foods, Medical and Agricultural Biotechnology.(June 2004).,I. C. Baianu, P. R. Lozano, V. I. Prisecaru and H. C. Lin q-bio/0406047 (http://arxiv.org/abs/q-bio/0406047)
[35] Chemical Imaging Without Dyeing (http://witec.de/en/download/Raman/ImagingMicroscopy04.pdf)
[36] C.L. Evans and X.S. Xie.2008. Coherent Anti-Stokes Raman Scattering Microscopy: Chemical Imaging for Biology and Medicine., doi:10.1146/annurev.anchem.1.031207.112754 *Annual Review of Analytical Chemistry*, **1**: 883-909.
[37] Eigen, M., Rigler, M. Sorting single molecules: application to diagnostics and evolutionary biotechnology,(1994) *Proc. Natl. Acad. Sci. USA*, 91,5740-5747.
[38] Rigler, M. Fluorescence correlations, single molecule detection and large number screening. Applications in biotechnology,(1995) J. Biotechnol., 41,177-186.
[39] Rigler R. and Widengren J. (1990). Ultrasensitive detection of single molecules by fluorescence correlation spectroscopy, *BioScience* (Ed. Klinge & Owman) p.180.

[40] Single Cancer Cell Detection by Near Infrared Microspectroscopy, Infrared Chemical Imaging and Fluorescence Microspectroscopy.2004.I. C. Baianu, D. Costescu, N. E. Hofmann, S. S. Korban and et al., q-bio/0407006 (July 2004) (http://arxiv.org/abs/q-bio/0407006)
[41] Oehlenschläger F., Schwille P. and Eigen M. (1996). Detection of HIV-1 RNA by nucleic acid sequence-based amplification combined with fluorescence correlation spectroscopy, *Proc. Natl. Acad. Sci. USA* **93**:1281.
[42] Bagatolli, L.A., and Gratton, E. (2000). Two-photon fluorescence microscopy of coexisting lipid domains in giant unilamellar vesicles of binary phospholipid mixtures. Biophys J., 78:290-305.
[43] Schwille, P., Haupts, U., Maiti, S., and Webb. W.(1999). Molecular dynamics in living cells observed by fluorescence correlation spectroscopy with one- and two-photon excitation. Biophysical Journal, 77(10):2251-2265.
[44] Near Infrared Microspectroscopy, Fluorescence Microspectroscopy,Infrared Chemical Imaging and High Resolution Nuclear Magnetic Resonance Analysis of Soybean Seeds, Somatic Embryos and Single Cells., Baianu, I.C. et al. 2004., In *Oil Extraction and Analysis.*, D. Luthria, Editor pp.241-273, AOCS Press., Champaign, IL.
[45] FRET description (http://dwb.unl.edu/Teacher/NSF/C08/C08Links/pps99.cryst.bbk.ac.uk/projects/gmocz/fret.htm)
[46] doi:10.1016/S0959-440X(00)00190-1 (http://dx.doi.org/10.1016/S0959-440X(00)00190-1)Recent advances in FRET: distance determination in protein–DNA complexes. *Current Opinion in Structural Biology* **2001**, *11(2)*, 201-207
[47] http://www.fretimaging.org/mcnamaraintro.html FRET imaging introduction
[48] Eigen, M., and Rigler, R. (1994). Sorting single molecules: Applications to diagnostics and evolutionary biotechnology, Proc. Natl. Acad. Sci. USA 91:5740.
[49] http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12379938
[50] Mao, Chengde; Sun, Weiqiong & Seeman, Nadrian C. (16 June 1999). "Designed Two-Dimensional DNA Holliday Junction Arrays Visualized by Atomic Force Microscopy". *Journal of the American Chemical Society* **121** (23): 5437–5443. doi: 10.1021/ja9900398 (http://dx.doi.org/10.1021/ja9900398). ISSN 0002-7863 (http://worldcat.org/issn/0002-7863).
[51] http://www.parkafm.com/New_html/resources/01general.php
[52] http://www.rhk-tech.com/results/showcase.php

References

- Sir Lawrence Bragg, FRS. *The Crystalline State, A General survey.* London: G. Bells and Sons, Ltd., vols. 1 and 2., 1966., 2024 pages.
- F. Bessel, *Untersuchung des Theils der planetarischen Störungen*, Berlin Abhandlungen (1824), article 14.
- Cantor, C. R. and Schimmel, P.R. *Biophysical Chemistry, Parts I and II.*, San Franscisco: W.H. Freeman and Co. 1980. 1,800 pages.
- Eigen, M., and Rigler, R. (1994). Sorting single molecules: Applications to diagnostics and evolutionary biotechnology, *Proc. Natl. Acad. Sci. USA* **91**:5740.
- Raghavachari, R., Editor. 2001. *Near-Infrared Applications in Biotechnology*, Marcel-Dekker, New York, NY.
- Rigler R. and Widengren J. (1990). Ultrasensitive detection of single molecules by fluorescence correlation spectroscopy, *BioScience* (Ed. Klinge & Owman) p.180.
- *Applications of Novel Techniques to Health Foods, Medical and Agricultural Biotechnology.*(June 2004) I. C. Baianu, P. R. Lozano, V. I. Prisecaru and H. C. Lin., q-bio/0406047.
- Single Cancer Cell Detection by Near Infrared Microspectroscopy, Infrared Chemical Imaging and Fluorescence Microspectroscopy.2004. I. C. Baianu, D. Costescu, N. E. Hofmann, S. S. Korban and et al., q-bio/0407006 (July 2004).
- Voet, D. and J.G. Voet. *Biochemistry*, 2nd Edn., New York, Toronto, Singapore: John Wiley & Sons, Inc., 1995, ISBN: 0-471-58651-X., 1361 pages.

- Watson, G. N. *A Treatise on the Theory of Bessel Functions.*, (1995) Cambridge University Press. ISBN 0-521-48391-3.
- Watson, James D. and Francis H.C. Crick. A structure for Deoxyribose Nucleic Acid (http://www.nature.com/nature/dna50/watsoncrick.pdf) (PDF). *Nature* 171, 737–738, 25 April 1953.
- Watson, James D. *Molecular Biology of the Gene.* New York and Amsterdam: W.A. Benjamin, Inc. 1965., 494 pages.
- Wentworth, W.E. *Physical Chemistry. A short course.*, Malden (Mass.): Blackwell Science, Inc. 2000.
- Herbert R. Wilson, FRS. *Diffraction of X-rays by proteins, Nucleic Acids and Viruses.*, London: Edward Arnold (Publishers) Ltd. 1966.
- Kurt Wuthrich. *NMR of Proteins and Nucleic Acids.*, New York, Brisbane,Chicester, Toronto, Singapore: J. Wiley & Sons. 1986., 292 pages.
- Robinson, Bruche H.; Seeman, Nadrian C. (August 1987). "The Design of a Biochip: A Self-Assembling Molecular-Scale Memory Device". *Protein Engineering* **1** (4): 295–300. ISSN 0269-2139 (http://worldcat.org/issn/0269-2139). Link (http://peds.oxfordjournals.org/cgi/content/abstract/1/4/295)
- Rothemund, Paul W. K.; Ekani-Nkodo, Axel; Papadakis, Nick; Kumar, Ashish; Fygenson, Deborah Kuchnir & Winfree, Erik (22 December 2004). "Design and Characterization of Programmable DNA Nanotubes". *Journal of the American Chemical Society* **126** (50): 16344–16352. doi: 10.1021/ja044319l (http://dx.doi.org/10.1021/ja044319l). ISSN 0002-7863 (http://worldcat.org/issn/0002-7863).
- Keren, K.; Kinneret Keren, Rotem S. Berman, Evgeny Buchstab, Uri Sivan, Erez Braun (November 2003). " DNA-Templated Carbon Nanotube Field-Effect Transistor (http://www.sciencemag.org/cgi/content/abstract/sci;302/5649/1380)". *Science* **302** (6549): 1380–1382. doi: 10.1126/science.1091022 (http://dx.doi.org/10.1126/science.1091022). ISSN 1095-9203 (http://worldcat.org/issn/1095-9203). http://www.sciencemag.org/cgi/content/abstract/sci;302/5649/1380.
- Zheng, Jiwen; Constantinou, Pamela E.; Micheel, Christine; Alivisatos, A. Paul; Kiehl, Richard A. & Seeman Nadrian C. (2006). "2D Nanoparticle Arrays Show the Organizational Power of Robust DNA Motifs". *Nano Letters* **6**: 1502–1504. doi: 10.1021/nl060994c (http://dx.doi.org/10.1021/nl060994c). ISSN 1530-6984 (http://worldcat.org/issn/1530-6984).
- Cohen, Justin D.; Sadowski, John P.; Dervan, Peter B. (2007). "Addressing Single Molecules on DNA Nanostructures". *Angewandte Chemie* **46** (42): 7956–7959. doi: 10.1002/anie.200702767 (http://dx.doi.org/10.1002/anie.200702767). ISSN 0570-0833 (http://worldcat.org/issn/0570-0833).
- Mao, Chengde; Sun, Weiqiong & Seeman, Nadrian C. (16 June 1999). "Designed Two-Dimensional DNA Holliday Junction Arrays Visualized by Atomic Force Microscopy". *Journal of the American Chemical Society* **121** (23): 5437–5443. doi: 10.1021/ja9900398 (http://dx.doi.org/10.1021/ja9900398). ISSN 0002-7863 (http://worldcat.org/issn/0002-7863).
- Constantinou, Pamela E.; Wang, Tong; Kopatsch, Jens; Israel, Lisa B.; Zhang, Xiaoping; Ding, Baoquan; Sherman, William B.; Wang, Xing; Zheng, Jianping; Sha, Ruojie & Seeman, Nadrian C. (2006). "Double cohesion in structural DNA nanotechnology". *Organic and Biomolecular Chemistry* **4**: 3414–3419. doi: 10.1039/b605212f (http://dx.doi.org/10.1039/b605212f).

See also

- → DNA
- → Molecular modeling of DNA
- Genomics
- Signal transduction
- Transcriptomics
- → Interactomics
- Biotechnology
- Molecular graphics
- Quantum computing
- MAYA-II
- DNA computing
- → DNA structure
- Molecular structure
- Molecular dynamics
- Molecular topology
- DNA topology
- DNA, the Genome and Interactome
- Molecular structure
- Molecular geometry fluctuations
- Molecular interactions
- Molecular topology
- Hydrogen bonding
- Hydrophobic interactions
- DNA dynamics and conformations
- DNA Conformational isomerism
- → 2D-FT NMRI and Spectroscopy
- Paracrystalline lattices/Paracrystals
- NMR Spectroscopy
- VCD or Vibrational circular dichroism
- Microwave spectroscopy
- Two-dimensional IR spectroscopy
- FRET and FCS- Fluorescence correlation spectroscopy
- Fluorescence cross-correlation spectroscopy (FCCS)
- Spectral imaging
- Hyperspectral imaging
- Chemical imaging
- NMR microscopy
- X-ray scattering
- Neutron scattering
- Crystallography
- Crystal lattices
- Molecular geometry
- Nanostructure
- → DNA nanotechnology
- Imaging
- Sirius visualization software

- Atomic force microscopy
- X-ray microscopy
- Liquid crystals
- Glasses
- QMC@Home
- Sir Lawrence Bragg, FRS
- Sir John Randall
- Francis Crick
- Manfred Eigen
- Felix Bloch
- Paul Lauterbur
- Maurice Wilkins
- Herbert Wilson, FRS
- Alex Stokes

External links

- DNAlive: a web interface to compute DNA physical properties (http://mmb.pcb.ub.es/DNAlive). Also allows cross-linking of the results with the UCSC Genome browser and DNA dynamics.
- Application of X-ray microscopy in analysis of living hydrated cells (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12379938)
- DiProDB: Dinucleotide Property Database (http://diprodb.fli-leibniz.de). The database is designed to collect and analyse thermodynamic, structural and other dinucleotide properties.
- DNA the Double Helix Game (http://nobelprize.org/educational_games/medicine/dna_double_helix/) From the official Nobel Prize web site
- MDDNA: Structural Bioinformatics of DNA (http://humphry.chem.wesleyan.edu:8080/MDDNA/)
- Double Helix 1953–2003 (http://www.ncbe.reading.ac.uk/DNA50/) National Centre for Biotechnology Education
- DNA under electron microscope (http://www.fidelitysystems.com/Unlinked_DNA.html)
- Further details of mathematical and molecular analysis of DNA structure based on X-ray data (http://planetphysics.org/encyclopedia/BesselFunctionsApplicationsToDiffractionByHelicalStructures.html)
- Bessel functions corresponding to Fourier transforms of atomic or molecular helices. (http://planetphysics.org/?op=getobj&from=objects&name=BesselFunctionsAndTheirApplicationsToDiffractionByHelicalStructures)
- Characterization in nanotechnology some pdfs (http://nanocharacterization.sitesled.com/)
- An overview of STM/AFM/SNOM principles with educative videos (http://www.ntmdt.ru/SPM-Techniques/Principles/)
- SPM Image Gallery - AFM STM SEM MFM NSOM and More (http://www.rhk-tech.com/results/showcase.php)
- How SPM Works (http://www.parkafm.com/New_html/resources/01general.php)
- U.S. National DNA Day (http://www.genome.gov/10506367) — watch videos and participate in real-time discusssions with scientists.

- The Secret Life of DNA - DNA Music compositions (http://www.tjmitchell.com/stuart/dna.html)
- Ascalaph DNA (http://www.agilemolecule.com/Ascalaph/Ascalaph_DNA.html) — Commercial software for DNA modeling

Vibrational spectroscopy

A **molecular vibration** occurs when atoms in a molecule are in periodic motion while the molecule as a whole has constant translational and rotational motion. The frequency of the periodic motion is known as a vibration frequency. A nonlinear molecule with n atoms has $3n-6$ normal modes of vibration, whereas a *linear* molecule has $3n-5$ normal modes of vibration as rotation about its molecular axis cannot be observed. A diatomic molecule thus has one normal mode of vibration. The normal modes of vibration of polyatomic molecules are independent of each other, each involving simultaneous vibrations of different parts of the molecule.

A molecular vibration is excited when the molecule absorbs a quantum of energy, E, corresponding to the vibration's frequency, ν, according to the relation $E=h\nu$, where h is Planck's constant. A fundamental vibration is excited when one such quantum of energy is absorbed by the molecule in its ground state. When two quanta are absorbed the first overtone is excited, and so on to higher overtones.

To a first approximation, the motion in a normal vibration can be described as a kind of simple harmonic motion. In this approximation, the vibrational energy is a quadratic function (parabola) with respect to the atomic displacements and the first overtone has twice the frequency of the fundamental. In reality, vibrations are anharmonic and the first overtone has a frequency that is slightly lower than twice that of the fundamental. Excitation of the higher overtones involves progressively less and less additional energy and eventually leads to dissociation of the molecule, as the potential energy of the molecule is more like a Morse potential.

The vibrational states of a molecule can be probed in a variety of ways. The most direct way is through infrared spectroscopy, as vibrational transitions typically require an amount of energy that corresponds to the infrared region of the spectrum. Raman spectroscopy, which typically uses visible light, can also be used to measure vibration frequencies directly.

Vibrational excitation can occur in conjunction with electronic excitation (vibronic transition), giving vibrational fine structure to electronic transitions, particularly with molecules in the gas state.

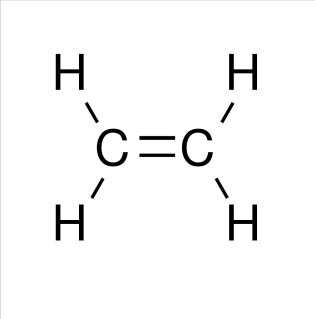
Simultaneous excitation of a vibration and rotations gives rise to vibration-rotation spectra.

Vibrational coordinates

The coordinate of a normal vibration is a combination of *changes* in the positions of atoms in the molecule. When the vibration is excited the coordinate changes sinusoidally with a frequency ν, the frequency of the vibration.

Internal coordinates

Internal coordinates are of the following types, illustrated with reference to the planar molecule ethylene,



- Stretching: a change in the length of a bond, such as C-H or C-C
- Bending: a change in the angle between two bonds, such as the HCH angle in a methylene group
- Rocking: a change in angle between a group of atoms, such as a methylene group and the rest of the molecule.
- Wagging: a change in angle between the plane of a group of atoms, such as a methylene group and a plane through the rest of the molecule,
- Twisting: a change in the angle between the planes of two groups of atoms, such as a change in the angle between the two methylene groups.
- Out-of-plane: Not present in ethene, but an example is in BF_3 when the boron atom moves in and out of the plane of the three fluorine atoms.

In a rocking, wagging or twisting coordinate the angles and bond lengths within the groups involved do not change. Rocking is distinguished from wagging by the fact that the atoms in the group stay in the same plane.

In ethene there are 12 internal coordinates: 4 C-H stretching, 1 C-C stretching, 2 H-C-H bending, 2 CH_2 rocking, 2 CH_2 wagging, 1 twisting. Note that the H-C-C angles cannot be used as internal coordinates as the angles at each carbon atom cannot all increase at the same time.

See infrared spectroscopy for some animated illustrations of internal coordinates.

Symmetry-adapted coordinates

Symmetry-adapted coordinates may be created by applying a projection operator to a set of internal coordinates.[1] The projection operator is constructed with the aid of the character table of the molecular point group. For example, the four(un-normalised) C-H stretching coordinates of the molecule ethene are given by

$$Q_{s1} = q_1 + q_2 + q_3 + q_4$$
$$Q_{s2} = q_1 + q_2 - q_3 - q_4$$
$$Q_{s3} = q_1 - q_2 + q_3 - q_4$$
$$Q_{s4} = q_1 - q_2 - q_3 + q_4$$

where q_1 - q_4 are the internal coordinates for stretching of each of the four C-H bonds.

Illustrations of symmetry-adapted coordinates for most small molecules can be found in Nakamoto.[2]

Normal coordinates

A normal coordinate, *Q*, may sometimes be constructed directly as a symmetry-adapted coordinate. This is possible when the normal coordinate belongs uniquely to a particular irreducible representation of the molecular point group. For example, the symmetry-adapted coordinates for bond-stretching of the linear carbon dioxide molecule, O=C=O are both normal coordinates:

- symmetric stretching: the sum of the two C-O stretching coordinates; the two C-O bond lengths change by the same amount and the carbon atom is stationary. $Q = q_1 + q_2$
- asymmetric stretching: the difference of the two C-O stretching coordinates; one C-O bond length increases while the other decreases. $Q = q_1 - q_2$

When two or more normal coordinates belong to the same irreducible representation of the molecular point group (colloquially, have the same symmetry) there is "mixing" and the coefficients of the combination cannot be determined *a priori*. For example, in the linear molecule hydrogen cyanide, HCN, The two stretching vibrations are

1. principally C-H stretching with a little C-N stretching; $Q_1 = q_1 + a\ q_2$ ($a << 1$)
2. principally C-N stretching with a little C-H stretching; $Q_2 = b\ q_1 + q_2$ ($b << 1$)

The coefficients a and b are found by performing a full normal coordinate analysis by means of the Wilson GF method.[3]

Newtonian mechanics

Perhaps surprisingly, molecular vibrations can be treated using Newtonian mechanics, to calculate the correct vibration frequencies. The basic assumption is that each vibration can be treated as though it corresponds to a spring. In the harmonic approximation the spring obeys Hooke's law: the force required to extend the spring is proportional to the extension. The proportionality constant is known as a *force constant, k*. The anharmonic oscillator is considered elsewhere.[4]

$$\text{Force} = -kQ$$

By Newton’s second law of motion this force is also equal to a "mass", *m*, times acceleration.

$$\text{Force} = m\frac{d^2Q}{dt^2}$$

Since this is one and the same force the ordinary differential equation follows.

$$m\frac{d^2Q}{dt^2} + kQ = 0$$

The solution to this equation of simple harmonic motion is

$$Q(t) = A\cos(2\pi\nu t); \quad \nu = \frac{1}{2\pi}\sqrt{\frac{k}{m}}$$

A is the maximum amplitude of the vibration coordinate *Q*. It remains to define the "mass", *m*. In a homonuclear diatomic molecule such as N_2, it is half the mass of one molecule. In a heteronuclear diatomic molecule, AB, it is the reduced mass, μ given by

$$\frac{1}{\mu} = \frac{1}{m_A} + \frac{1}{m_B}$$

The use of the reduced mass ensures that the centre of mass of the molecule is not affected by the vibration. In the harmonic approximation the potential energy of the molecule is a quadratic function of the normal coordinate. It follows that the force-constant is equal to the second derivative of the potential energy.

$$f = \frac{\partial^2 V}{\partial Q^2}$$

When two or more normal vibrations have the same symmetry a full normal coordinate analysis must be performed (see GF method). The vibration frequencies,ν_i are obtained from the eigenvalues,λ_i, of the matrix product ***GF***. ***G*** is a matrix of numbers derived from the masses of the atoms and the geometry of the molecule.[3] ***F*** is a matrix derived from force-constant values. Details concering the determination of the eigenvalues can be found in [5] .

Quantum mechanics

In the harmonic approximation the potential energy is a quadratic function of the normal coordinates. Solving the Schrödinger wave equation, the energy states for each normal coordinate are given by

$$E_n = \left(n + \frac{1}{2}\right) h\frac{1}{2\pi}\sqrt{\frac{k}{m}},$$

where *n* is a quantum number that can take values of 0, 1, 2 ... The difference in energy when *n* changes by 1 are therefore equal to the energy derived using classical mechanics. See quantum harmonic oscillator for graphs of the first 5 wave functions. Knowing the wave functions, certain selection rules can be formulated. For example, for a harmonic oscillator transitions are allowed only when the quantum number *n* changes by one,

$$\Delta n = \pm 1$$

but this does not apply to an anharmonic oscillator; the observation of overtones is only possible because vibrations are anharmonic. Another consequence of anharmonicity is that transitions such as between states *n*=2 and *n*=1 have slightly less energy than transitions between the ground state and first excited state. Such a transition gives rise to a hot band.

Intensities

In an infrared spectrum the intensity of an absorption band is proportional to the derivative of the molecular dipole moment with respect to the normal coordinate.[6] The intensity of Raman bands depends on polarizability. See also transition dipole moment.

See also

- Infrared spectroscopy
- Near infrared spectroscopy
- Raman spectroscopy
- Resonance Raman spectroscopy
- Coherent anti-Stokes Raman spectroscopy
- Eckart conditions
- FG method
- Fermi resonance

References

[1] F.A. Cotton *Chemical applications of group theory*, Wiley, 1962, 1971
[2] K. Nakamoto *Infrared and Raman spectra of inorganic and coordination compounds*, 5th. edition, Part A, Wiley, 1997
[3] E.B. Wilson, J.C. Decius and P.C. Cross, *Molecular vibrations*, McGraw-Hill, 1955. (Reprinted by Dover 1980)
[4] S. Califano, *Vibrational states*, Wiley, 1976
[5] P. Gans, *Vibrating molecules*, Chapman and Hall, 1971
[6] D. Steele, *Theory of vibrational spectroscopy*, W.B. Saunders, 1971

Further reading

- P.M.A. Sherwood, *Vibrational spectroscopy of solids*, Cambridge University Press, 1972

External links

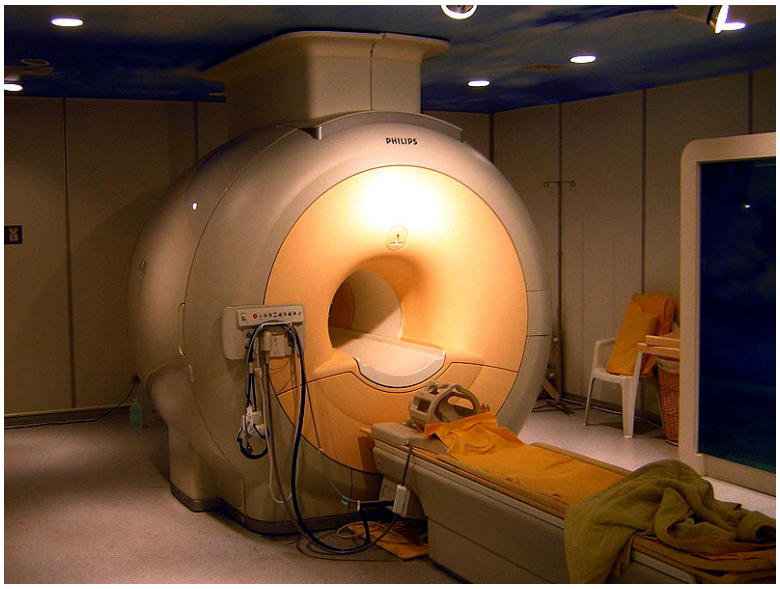
- Free Molecular Vibration code developed by Zs. Szabó and R. Scipioni (http://www.evtsz.bme.hu/web/staff/szabo/web_molecular_vibration/molec_vib_code.html)
- Molecular vibration and absorption (http://www.lsbu.ac.uk/water/vibrat.html)
- small explanation of vibrational spectra and a table including force constants (http://hyperphysics.phy-astr.gsu.edu/Hbase/molecule/vibspe.html).
- Character tables for chemically important point groups (http://symmetry.jacobs-university.de/)

2D-FT NMRI and Spectroscopy

2D-FT Nuclear magnetic resonance imaging (**2D-FT NMRI**), or **Two-dimensional Fourier transform** nuclear magnetic resonance imaging (**NMRI**), is primarily a non—invasive imaging technique most commonly used in biomedical research and medical radiology/nuclear medicine/MRI to visualize structures and functions of the living systems and single cells. For example it can provides fairly detailed images of a human body in any selected cross-sectional plane, such as longitudinal, transversal, sagital, etc. The basic NMR phenomenon or physical principle[1] is essentially the same in N(MRI), nuclear magnetic resonance/FT (NMR) spectroscopy, topical NMR, or even in Electron Spin Resonance /EPR; however, the details are significantly different at present for EPR, as only in the early days of NMR the static magnetic field was scanned for obtaining spectra, as it is still the case in many EPR or ESR spectrometers. NMRI, on the other hand, often utilizes a linear magnetic field gradient to obtain an image that combines the visualization of molecular structure and dynamics. It is this dynamic aspect of NMRI, as well as its highest sensitivity for the ^{1}H nucleus that distinguishes it very dramatically from X-ray CAT scanning that 'misses' hydrogens because of their very low X-ray scattering factor.

Thus, NMRI provides much greater contrast especially for the different soft tissues of the body than computed tomography (CT) as its most sensitive option observes the nuclear spin distribution and dynamics of highly mobile molecules that contain the naturally abundant, stable hydrogen isotope ^{1}H as in plasma water molecules, blood, disolved metabolites and fats. This approach makes it most useful in cardiovascular, oncological (cancer), neurological (brain), musculoskeletal, and cartilage imaging. Unlike CT, it uses no ionizing radiation, and also unlike nuclear imaging it does not employ any radioactive isotopes. Some of the first MRI images reported were published in 1973[2] and the first study performed on a human took place on July 3, 1977.[3] Earlier papers were also published by Sir Peter Mansfield[4] in UK (Nobel Laureate in 2003), and R. Damadian in the USA[5] , (together with an approved patent for 'fonar', or magnetic imaging). The detailed physical theory of NMRI was published by Peter Mansfield in 1973[6] . Unpublished 'high-resolution' (50 micron resolution) images of other living systems, such as hydrated wheat grains, were also obtained and communicated in UK in 1977-1979, and were subsequently confirmed by articles published in *Nature* by Peter Callaghan.

NMR Principle



Advanced 4.7 T clinical diagnostics and biomedical research NMR Imaging instrument.

Certain nuclei such as ^{1}H nuclei, or `fermions' have spin-1/2, because there are two spin states, referred to as "up" and "down" states. The nuclear magnetic resonance absorption phenomenon occurs when samples containing such nuclear spins are placed in a static magnetic field and a very short radiofrequency pulse is applied with a center, or carrier, frequency matching that of the transition between the up and down states of the spin-1/2 ^{1}H nuclei that were polarized by the static magnetic field. [7] Very low field schemes have also been recently reported.[8]

Chemical Shifts

NMR is a very useful family of techniques for chemical and biochemical research because of the chemical shift; this effect consists in a frequency shift of the nuclear magnetic resonance for specific chemical groups or atoms as a result of the partial shielding of the corresponding nuclei from the applied, static external magnetic field by the electron orbitals (or molecular orbitals) surrounding such nuclei present in the chemical groups. Thus, the higher the electron density surrounding a specific nucleus the larger the chemical shift will be. The resulting magnetic field at the nucleus is thus lower than the applied external magnetic field and the resonance frequencies observed as a result of such shielding are lower than the value that would be observed in the absence of any electronic orbital shielding. Furthermore, in order to obtain a chemical shift value independent of the strength of the applied magnetic field and allow for the direct comparison of spectra obtained at different magnetic field values, the chemical shift is defined by the ratio of the strength of the local magnetic field value at the observed (electron orbital-shielded) nucleus by the external magnetic field strength, $\mathbf{H}_{loc}/\ \mathbf{H}_{0}$. The first NMR observations of the chemical shift, with the correct physical chemistry interpretation, were reported for ^{19}F containing compounds in the early 1950s by Herbert S. Gutowsky and Charles P. Slichter from the University of Illinois at Urbana (USA).

A related effect in metals is called the Knight shift, which is due only to the conduction electrons. Such conduction electrons present in metals induce an "additional" local field at the nuclear site, due to the spin re-orientation of the conduction electrons in the presence of the applied (constant), external magnetic field. This is only broadly `similar' to the chemical shift in either solutions or diamagnetic solids.

NMR Imaging Principles

A number of methods have been devised for combining magnetic field gradients and radiofrequency pulsed excitation to obtain an image. Two major maethods involve either 2D -FT or 3D-FT[9] reconstruction from projections, somewhat similar to Computed Tomography, with the exception of the image interpretation that in the former case must include dynamic and relaxation/contrast enhancement information as well. Other schemes involve building the NMR image either point-by-point or line-by-line. Some schemes use instead gradients in the rf field rather than in the static magnetic field. The majority of NMR images routinely obtained are either by the Two-Dimensional Fourier Transform (2D-FT) technique [10] (with slice selection), or by the Three-Dimensional Fourier Transform (3D—FT) techniques that are however much more time consuming at present. 2D-FT NMRI is sometime called in common parlance a "spin-warp". An NMR image corresponds to a spectrum consisting of a number of `spatial frequencies' at different locations in the sample investigated, or in a patient.[11] A two–dimensional Fourier transformation of such a "real" image may be considered as a representation of such "real waves" by a matrix of spatial frequencies known as the k–space. We shall see next in some mathematical detail how the 2D-FT computation works to obtain 2D-FT NMR images.

Two-dimensional Fourier transform imaging and spectroscopy

A two-dimensional Fourier transform (2D-FT) is computed numerically or carried out in two stages, both involving `standard', one-dimensional Fourier transforms. However, the second stage Fourier transform is not the inverse Fourier transform (which would result in the original function that was transformed at the first stage), but a Fourier transform in a second variable—which is `shifted' in value—relative to that involved in the result of the first Fourier transform. Such 2D-FT analysis is a very powerful method for both NMRI and two-dimensional nuclear magnetic resonance spectroscopy (2D-FT NMRS)[12] that allows the three-dimensional reconstruction of polymer and biopolymer structures at atomic resolution.[13] for molecular weights (Mw) of dissolved biopolymers in aqueous solutions (for example) up to about 50,000 Mw. For larger biopolymers or polymers, more complex methods have been developed to obtain limited structural resolution needed for partial 3D-reconstructions of higher molecular structures, e.g. for up 900,000 Mw or even oriented microcrystals in aqueous suspensions or single crystals; such methods have also been reported for *in vivo* 2D-FT NMR spectroscopic studies of algae, bacteria, yeast and certain mammalian cells, including human ones. The 2D-FT method is also widely utilized in optical spectroscopy, such as *2D-FT NIR hyperspectral imaging* (2D-FT NIR-HS), or in MRI imaging for research and clinical, diagnostic applications in Medicine. In the latter case, 2D-FT NIR-HS has recently allowed the identification of single, malignant cancer cells surrounded by healthy human breast tissue at about 1 micron resolution, well-beyond the resolution obtainable by 2D-FT NMRI for such systems in the limited time available for such diagnostic investigations (and also in magnetic fields up to the FDA approved magnetic field strength $\mathbf{H}_0$ of 4.7 T, as shown in the top image of the state-of-the-art NMRI instrument). A more precise mathematical definition of the `double' (2D) Fourier transform involved in both 2D NMRI and 2D-FT NMRS is specified next, and a precise example follows this generally accepted definition.

2D-FT Definition

A *2D-FT, or two-dimensional Fourier transform*, is a standard Fourier transformation of a function of two variables, **f**(x_1, x_2), carried first in the first variable x_1, followed by the Fourier transform in the second variable x_2 of the resulting function **F**(s_1,x_2). Note that in the case of both 2D-FT NMRI and 2D-FT NMRS the two independent variables in this definition are in the time domain, whereas the results of the two successive Fourier transforms have, of course, frequencies as the independent variable in the NMRS, and ultimately spatial coordinates for both 2D NMRI and 2D-FT NMRS following computer structural recontructions based on special algorithms that are different from FT or 2D-FT. Moreover, such structural algorithms are different for 2D NMRI and 2D-FT NMRS: in the former case they involve macroscopic, or anatomical structure detrmination, whereas in the latter case of 2D-FT NMRS the atomic structure reconstruction algorithms are based on the quantum theory of a microphysical (quantum) process such as nuclear Overhauser enhancement NOE, or specific magnetic dipole-dipole interactions[14] between neighbor nuclei.

Example 1

A 2D Fourier transformation and phase correction is applied to a set of 2D NMR (FID) signals: **s**(t_1,t_2) yielding a real 2D-FT NMR `spectrum' (collection of 1D FT-NMR spectra) represented by a matrix **S** whose elements are

$$\mathbf{S}\ (\nu_1, \nu_2) = \mathbf{Re} \int \int cos(\nu_1 t_1) exp^{(-i\nu_2 t_2)} s(t_1, t_2) dt_1 dt_2$$

where : ν_1 and : ν_2 denote the discrete indirect double-quantum and single-quantum(detection) axes, respectively, in the 2D NMR experiments. Next, the *covariance matrix* is calculated in the frequency domain according to the following equation

C $(\nu_2', \nu_2) = S^T S = \sum_{\nu^1} [S(\nu_1, \nu_2') S(\nu_1, \nu_2)],$ with : ν_2, ν_2' taking all possible single-quantum frequency values and with the summation carried out over all discrete, double quantum frequencies : ν_1.

Example 2

Atomic Structure from 2D-FT STEM Images [15] of electron distributions in a high-temperature cuprate superconductor `paracrystal' reveal both the domains (or `location') and the local symmetry of the 'pseudo-gap' in the electron-pair correlation band responsible for the high—temperature superconductivity effect (obtained at Cornell University). So far there have been three Nobel prizes awarded for 2D-FT NMR/MRI during 1992-2003, and an additional, earlier Nobel prize for 2D-FT of X-ray data (`CAT scans'); recently the advanced possibilities of 2D-FT techniques in Chemistry, Physiology and Medicine [16] received very significant recognition.[17]

Brief explanation of NMRI diagnostic uses in Pathology

As an example, a diseased tissue such as a malign tumor, can be detected by 2D-FT NMRI because the hydrogen nuclei of molecules in different tissues return to their equilibrium spin state at different relaxation rates, and also because of the manner in which a malign tumor spreads and grows rapidly along the blood vessels adjacent to the tumor, also inducing further vascularization to occur. By changing the pulse delays in the RF pulse

sequence employed, and/or the RF pulse sequence itself, one may obtain a `relaxation—based contrast', or contrast enhancement between different types of body tissue, such as normal vs. diseased tissue cells for example. Excluded from such diagnostic observations by NMRI are all patients with ferromagnetic metal implants, (e.g., cochlear implants), and all cardiac pacemaker patients who cannot undergo any NMRI scan because of the very intense magnetic and RF fields employed in NMRI which would strongly interfere with the correct functioning of such pacemakers. It is, however, conceivable that future developments may also include along with the NMRI diagnostic treatments with special techniques involving applied magnetic fields and very high frequency RF. Already, surgery with special tools is being experimented on in the presence of NMR imaging of subjects.Thus, NMRI is used to image almost every part of the body, and is especially useful for diagnosis in neurological conditions, disorders of the muscles and joints, for evaluating tumors, such as in lung or skin cancers, abnormalities in the heart (especially in children with hereditary disorders), blood vessels, CAD, atherosclerosis and cardiac infarcts [18] (courtesy of Dr. Robert R. Edelman)

See also

- Nuclear magnetic resonance (NMR)
- Edward Mills Purcell
- Felix Bloch
- Medical imaging
- Paul C. Lauterbur
- Magnetic resonance microscopy
- Peter Mansfield
- Computed tomography (CT)
- Solid-state NMR
- Knight shift
- John Hasbrouck Van Vleck
- Chemical shift
- Herbert S. Gutowsky
- John S. Waugh
- Charles Pence Slichter
- Protein nuclear magnetic resonance spectroscopy
- Kurt Wüthrich
- Nuclear Overhauser effect
- Fourier transform spectroscopy(FTS)
- Jean Jeneer
- Richard R. Ernst
- FT-NIRS (NIR)
- Magnetic resonance elastography
- Relaxation
- Earth's field NMR (EFNMR)
- Robinson oscillator

Footnotes

[1] Antoine Abragam. 1968. *Principles of Nuclear Magnetic Resonance.*, 895 pp., Cambridge University Press: Cambridge, UK.

[2] Lauterbur, P.C., Nobel Laureate in 2003 (1973). "Image Formation by Induced Local Interactions: Examples of Employing Nuclear Magnetic Resonance". *Nature* **242**: 190–1. doi: 10.1038/242190a0 (http://dx.doi.org/10.1038/242190a0).

[3] Howstuffworks "How MRI Works" (http://www.howstuffworks.com/mri.htm/printable)

[4] Peter Mansfield. 2003. Nobel Laureate in Physiology and Medicine for (2D and 3D) MRI (http://www.parteqinnovations.com/pdf-doc/fandr-Gaz1006.pdf)

[5] Damadian, R. V. "Tumor Detection by Nuclear Magnetic Resonance," Science, 171 (March 19, 1971): 1151-1153 (http://www.sciencemag.org/cgi/content/abstract/171/3976/1151)

[6] NMR 'diffraction' in solids? P. Mansfield et al. 1973 J. Phys. C: Solid State Phys. 6 L422-L426 doi: 10.1088/0022-3719 (http://www.iop.org/EJ/article/0022-3719/6/22/007/jcv6i22pL422.pdf)

[7] Antoine Abragam. 1968. *Principles of Nuclear Magnetic Resonance.*, 895 pp., Cambridge University Press: Cambridge, UK.

[8] Raftery D (August 2006). " MRI without the magnet (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=1568902)". *Proc Natl Acad Sci USA.* **103** (34): 12657–8. doi: 10.1073/pnas.0605625103 (http://dx.doi.org/10.1073/pnas.0605625103). PMID 16912110.

[9] Wu Y, Chesler DA, Glimcher MJ, *et al.* (February 1999). " Multinuclear solid-state three-dimensional MRI of bone and synthetic calcium phosphates (http://www.pnas.org/cgi/pmidlookup?view=long&pmid=9990066)". *Proc. Natl. Acad. Sci. U.S.A.* **96** (4): 1574–8. doi: 10.1073/pnas.96.4.1574 (http://dx.doi.org/10.1073/pnas.96.4.1574). PMID 9990066. PMC: 15521 (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=15521). .

[10] http://www.math.cuhk.edu.hk/course/mat2071a/lec1_08.ppt

[11] *Haacke, E Mark; Brown, Robert F; Thompson, Michael; Venkatesan, Ramesh (1999). *Magnetic resonance imaging: physical principles and sequence design*. New York: J. Wiley & Sons. ISBN 0-471-35128-8.

[12] Richard R. Ernst. 1992. Nuclear Magnetic Resonance Fourier Transform (2D-FT) Spectroscopy. Nobel Lecture (http://nobelprize.org/nobel_prizes/chemistry/laureates/1991/ernst-lecture.pdf), on December 9, 1992.

[13] http://en.wikipedia.org/wiki/Nuclear_magnetic_resonance#Nuclear_spin_and_magnets Kurt Wüthrich in 1982-1986 : 2D-FT NMR of solutions

[14] Charles P. Slichter.1996. *Principles of Magnetic Resonance.* Springer: Berlin and New York, Third Edition., 651pp. ISBN 0-387-50157-6.

[15] http://www.physorg.com/news129395045.html

[16] http://nobelprize.org/nobel_prizes/chemistry/laureates/1991/ernst-lecture.pdf

[17] Protein structure determination in solution by NMR spectroscopy (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=2266107&query_hl=33&itool=pubmed_docsum) Kurt Wüthrich. J Biol Chem. 1990 December 25;265(36):22059-62.

[18] http://www.mr-tip.com/serv1.php?type=img&img=Cardiac%20Infarct%20Short%20Axis%20Cine%204

References

- Antoine Abragam. 1968. *Principles of Nuclear Magnetic Resonance.*, 895 pp., Cambridge University Press: Cambridge, UK.
- Charles P. Slichter.1996. *Principles of Magnetic Resonance.* Springer: Berlin and New York, Third Edition., 651pp. ISBN 0-387-50157-6.
- Kurt Wüthrich. 1986, *NMR of Proteins and Nucleic Acids.*, J. Wiley and Sons: New York, Chichester, Brisbane, Toronto, Singapore. (Nobel Laureate in 2002 for 2D-FT NMR Studies of Structure and Function of Biological Macromolecules (http://nobelprize.org/nobel_prizes/chemistry/laureates/2002/wutrich-lecture.pdf)
- Protein structure determination in solution by NMR spectroscopy (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=2266107&query_hl=33&itool=pubmed_docsum) Kurt Wüthrich. J Biol Chem. 1990 December 25;265(36):22059-62

- 2D-FT NMRI Instrument image: A JPG color image of a 2D-FT NMRI `monster' Instrument (http://upload.wikimedia.org/wikipedia/en/b/bf/HWB-NMRv900.jpg).
- Richard R. Ernst. 1992. Nuclear Magnetic Resonance Fourier Transform (2D-FT) Spectroscopy. Nobel Lecture (http://nobelprize.org/nobel_prizes/chemistry/laureates/1991/ernst-lecture.pdf), on December 9, 1992.
- Peter Mansfield. 2003. Nobel Laureate in Physiology and Medicine for (2D and 3D) MRI (http://www.parteqinnovations.com/pdf-doc/fandr-Gaz1006.pdf)
- D. Benett. 2007. PhD Thesis. Worcester Polytechnic Institute. PDF of 2D-FT Imaging Applications to NMRI in Medical Research. (http://www.wpi.edu/Pubs/ETD/Available/etd-081707-080430/unrestricted/dbennett.pdf) Worcester Polytechnic Institute. (Includes many 2D-FT NMR images of human brains.)
- Paul Lauterbur. 2003. Nobel Laureate in Physiology and Medicine for (2D and 3D) MRI. (http://nobelprize.org/nobel_prizes/medicine/laureates/2003/)
- Jean Jeener. 1971. Two-dimensional Fourier Transform NMR, presented at an Ampere International Summer School, Basko Polje, unpublished. A verbatim quote follows from Richard R. Ernst's Nobel Laureate Lecture delivered on December 2, 1992, "A new approach to measure two-dimensional (2D) spectra." has been proposed by Jean Jeener at an Ampere Summer School in Basko Polje, Yugoslavia, 1971 (Jean Jeneer,1971)). He suggested a 2D Fourier transform experiment consisting of two $\pi/2$ pulses with a variable time t_1 between the pulses and the time variable t_2 measuring the time elapsed after the second pulse as shown in Fig. 6 that expands the principles of Fig. 1. Measuring the response $s(t_1,t_2)$ of the two-pulse sequence and Fourier-transformation with respect to both time variables produces a two-dimensional spectrum $S(O_1,O_2)$ of the desired form. This two-pulse experiment by Jean Jeener is the forefather of a whole class of $2D$ experiments that can also easily be expanded to multidimensional spectroscopy.
- Dudley, Robert, L (1993). "High-Field NMR Instrumentation". *Ch. 10 in Physical Chemistry of Food Processes* (New York: Van Nostrand-Reinhold) **2**: 421-30. ISBN 0-442-00582-2.
- Baianu, I.C.; Kumosinski, Thomas (August 1993). "NMR Principles and Applications to Structure and Hydration,". *Ch.9 in Physical Chemistry of Food Processes* (New York: Van Nostrand-Reinhold) **2**: 338-420. ISBN 0-442-00582-2.
- Haacke, E Mark; Brown, Robert F; Thompson, Michael; Venkatesan, Ramesh (1999). *Magnetic resonance imaging: physical principles and sequence design*. New York: J. Wiley & Sons. ISBN 0-471-35128-8.
- Raftery D (August 2006). " MRI without the magnet (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=1568902)". *Proc Natl Acad Sci USA.* **103** (34): 12657–8. doi: 10.1073/pnas.0605625103 (http://dx.doi.org/10.1073/pnas.0605625103). PMID 16912110.
- Wu Y, Chesler DA, Glimcher MJ, *et al.* (February 1999). " Multinuclear solid-state three-dimensional MRI of bone and synthetic calcium phosphates (http://www.pnas.org/cgi/pmidlookup?view=long&pmid=9990066)". *Proc. Natl. Acad. Sci. U.S.A.* **96** (4): 1574–8. doi: 10.1073/pnas.96.4.1574 (http://dx.doi.org/10.1073/pnas.96.4.1574). PMID 9990066. PMC: 15521 (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pmcentrez&artid=15521). http://www.pnas.org/cgi/pmidlookup?view=long&

pmid=9990066.

External links

- Cardiac Infarct or "heart attack" Imaged in Real Time by 2D-FT NMRI (http://www.mr-tip.com/exam_gifs/cardiac_infarct_short_axis_cine_6.gif)
- Interactive Flash Animation on MRI (http://www.e-mri.org) - *Online Magnetic Resonance Imaging physics and technique course*
- Herbert S. Gutowsky
- Jiri Jonas and Charles P. Slichter: NMR Memoires at NAS about Herbert Sander Gutowsky; NAS = National Academy of Sciences, USA, (http://books.nap.edu/html/biomems/hgutowsky.pdf)
- 3D Animation Movie about MRI Exam (http://www.patiencys.com/MRI/)
- International Society for Magnetic Resonance in Medicine (http://www.ismrm.org)
- Danger of objects flying into the scanner (http://www.simplyphysics.com/flying_objects.html)

Related Wikipedia websites

- Medical imaging
- Computed tomography
- Magnetic resonance microscopy
- Fourier transform spectroscopy
- FT-NIRS
- Chemical imaging
- Magnetic resonance elastography
- Nuclear magnetic resonance (NMR)
- Chemical shift
- Relaxation
- Robinson oscillator
- Earth's field NMR (EFNMR)
- Rabi cycle

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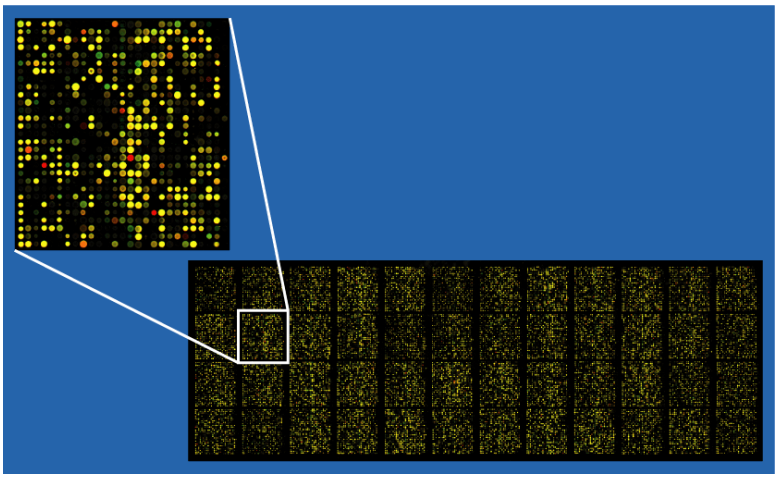
DNA Technologies

DNA microarray

For terminology, see glossary below.



Example of an approximately 40,000 probe spotted oligo microarray with enlarged inset to show detail.

A **DNA microarray** is a multiplex technology used in molecular biology and in medicine. It consists of an arrayed series of thousands of microscopic spots of → DNA oligonucleotides, called features, each containing picomoles of a specific DNA sequence. This can be a short section of a gene or other DNA element that are used as probes to hybridize a cDNA or cRNA sample (called target) under high-stringency conditions. Probe-target hybridization is usually detected and quantified by detection of fluorophore-, silver-, or chemiluminescence-labeled targets to determine relative abundance of nucleic acid sequences in the target.

In standard microarrays, the probes are attached to a solid surface by a covalent bond to a chemical matrix (via epoxy-silane, amino-silane, lysine, polyacrylamide or others). The solid surface can be glass or a silicon chip, in which case they are commonly known as *gene chip* or colloquially *Affy chip* when an Affymetrix chip is used. Other microarray platforms, such as Illumina, use microscopic beads, instead of the large solid support. DNA arrays are different from other types of microarray only in that they either measure DNA or use DNA as part of its detection system.

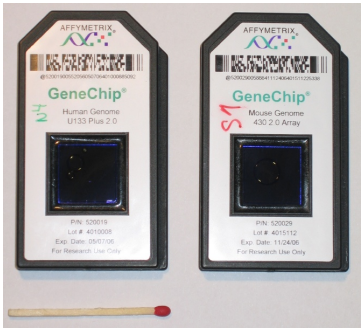
DNA microarrays can be used to measure changes in expression levels, to detect single nucleotide polymorphisms (SNPs) (*see uses and types section*), in genotyping or in resequencing mutant genomes. Microarrays also differ in fabrication, workings, accuracy, efficiency, and cost (*see fabrication section*). Additional factors for microarray experiments are the experimental design and the methods of analyzing the data (*see Bioinformatics section*).

History

Microarray technology evolved from Southern blotting, where fragmented DNA is attached to a substrate and then probed with a known gene or fragment. The use of a collection of distinct DNAs in arrays for expression profiling was first described in 1987, and the arrayed DNAs were used to identify genes whose expression is modulated by interferon.[1] These early gene arrays were made by spotting cDNAs onto filter paper with a pin-spotting device. The use of miniaturized microarrays for gene expression profiling was first reported in 1995, [2] and a complete eukaryotic genome (*Saccharomyces cerevisiae*) on a microarray was published in 1997. [3]

Uses and types

Arrays of DNA can be spatially arranged, as in the commonly known *gene chip* (also called *genome chip*, *DNA chip* or *gene array*), or can be specific DNA sequences labelled such that they can be independently identified in solution. The traditional solid-phase array is a collection of microscopic → DNA spots attached to a solid surface, such as glass, plastic or silicon biochip. The affixed DNA segments are known as *probes* (although some sources use different terms such as *reporters*). Thousands of them can be placed in known locations on a single DNA microarray.



Two Affymetrix chips

DNA microarrays can be used to detect DNA (as in comparative genomic hybridization), or detect RNA (most commonly as cDNA after reverse transcription) that may or may not be translated into proteins. The process of measuring gene expression via cDNA is called expression analysis or expression profiling.

Since an array can contain tens of thousands of probes, a microarray experiment can accomplish that many genetic tests in parallel. Therefore arrays have dramatically accelerated many types of investigation.

Applications include:

Technology or Application	Synopsis
Gene expression profiling	In an mRNA or gene expression profiling experiment the expression levels of thousands of genes are simultaneously monitored to study the effects of certain treatments, diseases, and developmental stages on gene expression. For example, microarray-based gene expression profiling can be used to identify genes whose expression is changed in response to pathogens or other organisms by comparing gene expression in infected to that in uninfected cells or tissues. [4]
Comparative genomic hybridization	Assessing genome content in different cells or closely related organisms. [5] [6]
GeneID	Small microarrays to check IDs of organisms in food and feed (like GMO [7]), mycoplasms in cell culture, or pathogens for disease detection, mostly combining PCR and microarray technology.

Chromatin immunoprecipitation on Chip	DNA sequences bound to a particular protein can be isolated by immunoprecipitating that protein (ChIP), these fragments can be then hybridized to a microarray (such as a tiling array) allowing the determination of protein binding site occupancy throughout the genome. Example protein to immunoprecipitate are histone modifications (H3K27me3, H3K4me2, H3K9me3, etc), Polycomb-group protein (PRC2:Suz12, PRC1:YY1) and trithorax-group protein (Ash1) to study the epigenetic landscape or RNA Polymerase II to study the transcription landscape.
SNP detection	Identifying single nucleotide polymorphism among alleles within or between populations.[8] Several applications of microarrays make use of SNP detection, including Genotyping, forensic analysis, measuring predisposition to disease, identifying drug-candidates, evaluating germline mutations in individuals or somatic mutations in cancers, assessing loss of heterozygosity, or genetic linkage analysis.
Alternative splicing detection	An '*exon junction array* design uses probes specific to the expected or potential splice sites of predicted exons for a gene. It is of intermediate density, or coverage, to a typical gene expression array (with 1-3 probes per gene) and a genomic tiling array (with hundreds or thousands of probes per gene). It is used to assay the expression of alternative splice forms of a gene. Exon arrays have a different design, employing probes designed to detect each individual exon for known or predicted genes, and can be used for detecting different splicing isoforms.
Tiling array	Genome tiling arrays consist of overlapping probes designed to densely represent a genomic region of interest, sometimes as large as an entire human chromosome. The purpose is to empirically detect expression of transcripts or alternatively splice forms which may not have been previously known or predicted.

Fabrication

Microarrays can be manufactured in different ways, depending on the number of probes under examination, costs, customization requirements, and the type of scientific question being asked. Arrays may have as few as 10 probes or up to 2.1 million (NimbleGen, Roche) micrometre-scale probes from commercial vendors.

Surface engineering

The first step of DNA microarray fabrication involves surface engineering of a substrate in order to obtain desirable surface properties for the application of interest. Optimal surface properties are those which produce high signal to noise ratios for the DNA targets of interest. Generally, this involves maximizing the probe surface density and activity while minimizing the non-specific binding of the targets of interest. Methods of surface engineering vary depending on the platform material, design, and application.

Spotted vs.oligonucleotide arrays

Microarrays can be fabricated using a variety of technologies, including printing with fine-pointed pins onto glass slides, photolithography using pre-made masks, photolithography using dynamic micromirror devices, ink-jet printing,[9] or electrochemistry on microelectrode arrays.

In *spotted microarrays*, the probes are oligonucleotides, cDNA or small fragments of PCR products that correspond to mRNAs. The probes are synthesized prior to deposition on the array surface and are then "spotted" onto glass. A common approach utilizes an array of fine pins or needles controlled by a robotic arm that is dipped into wells containing DNA probes and then depositing each probe at designated locations on the array surface. The resulting "grid" of probes represents the nucleic acid profiles of the prepared probes and is ready to receive complementary cDNA or cRNA "targets" derived from experimental or clinical samples. This technique is used by research scientists around the world to produce "in-house" printed microarrays from their own labs. These arrays may be easily customized for each experiment, because researchers can choose the probes and printing locations on the arrays, synthesize the probes in their own lab (or collaborating facility), and spot the arrays. They can then generate their own labeled samples for hybridization, hybridize the samples to the array, and finally scan the arrays with their own equipment. This provides a relatively low-cost microarray that may be customized for each study, and avoids the costs of purchasing often more expensive commercial arrays that may represent vast numbers of genes that are not of interest to the investigator. Publications exist which indicate in-house spotted microarrays may not provide the same level of sensitivity compared to commercial oligonucleotide arrays,[10] possibly owing to the small batch sizes and reduced printing efficiencies when compared to industrial manufactures of oligo arrays.

In *oligonucleotide microarrays*, the probes are short sequences designed to match parts of the sequence of known or predicted open reading frames. Although oligonucleotide probes are often used in "spotted" microarrays, the term "oligonucleotide array" most often refers to a specific technique of manufacturing. Oligonucleotide arrays are produced by printing short oligonucleotide sequences designed to represent a single gene or family of gene splice-variants by synthesizing this sequence directly onto the array surface instead of depositing intact sequences. Sequences may be longer (60-mer probes such as the Agilent design) or shorter (25-mer probes produced by Affymetrix) depending on the desired purpose; longer probes are more specific to individual target genes, shorter probes may be spotted in higher density across the array and are cheaper to manufacture. One technique used to produce oligonucleotide arrays include photolithographic synthesis (Agilent and Affymetrix) on a silica substrate where light and light-sensitive masking agents are used to "build" a sequence one nucleotide at a time across the entire array.[11] Each applicable probe is selectively "unmasked" prior to bathing the array in a solution of a single nucleotide, then a masking reaction takes place and the next set of probes are unmasked in preparation for a different nucleotide exposure. After many repetitions, the sequences of every probe become fully constructed. More recently, Maskless Array Synthesis from NimbleGen Systems has combined flexibility with large numbers of probes.[12]

Two-channel vs.one-channel detection

Two-color microarrays or *two-channel microarrays* are typically hybridized with cDNA prepared from two samples to be compared (e.g. diseased tissue versus healthy tissue) and that are labeled with two different fluorophores.[13] Fluorescent dyes commonly used for cDNA labelling include Cy3, which has a fluorescence emission wavelength of 570 nm (corresponding to the green part of the light spectrum), and Cy5 with a fluorescence emission wavelength of 670 nm (corresponding to the red part of the light spectrum). The two Cy-labelled cDNA samples are mixed and hybridized to a single microarray that is then scanned in a microarray scanner to visualize fluorescence of the two fluorophores after excitation with a laser beam of a defined wavelength. Relative intensities of each fluorophore may then be used in ratio-based analysis to identify up-regulated and down-regulated genes.[14]

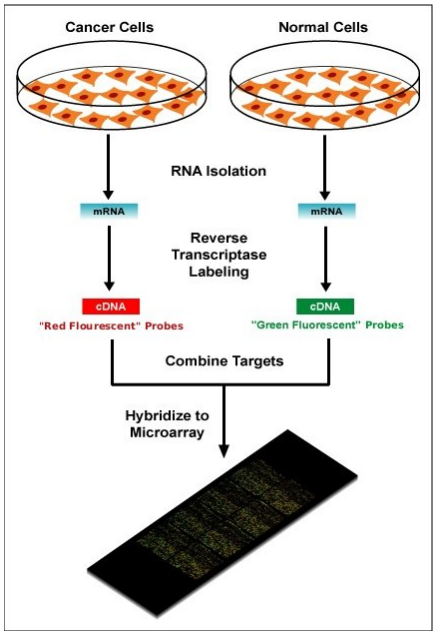


Diagram of typical dual-colour microarray experiment.

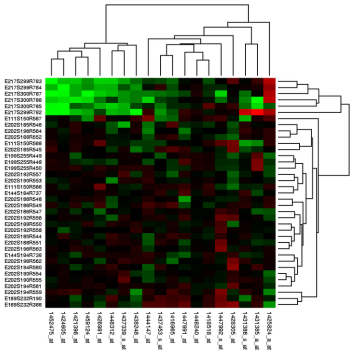
Oligonucleotide microarrays often contain control probes designed to hybridize with RNA spike-ins. The degree of hybridization between the spike-ins and the control probes is used to normalize the hybridization measurements for the target probes. Although absolute levels of gene expression may be determined in the two-color array, the relative differences in expression among different spots within a sample and between samples is the preferred method of data analysis for the two-color system. Examples of providers for such microarrays includes Agilent with their Dual-Mode platform, Eppendorf with their DualChip platform for colorimetric Silverquant labeling, and TeleChem International with Arrayit.

In *single-channel microarrays* or *one-color microarrays*, the arrays are designed to give estimations of the absolute levels of gene expression. Therefore the comparison of two conditions requires two separate single-dye hybridizations. As only a single dye is used, the data collected represent absolute values of gene expression. These may be compared to other genes within a sample or to reference "normalizing" probes used to calibrate data across the entire array and across multiple arrays. Three popular single-channel systems are the Affymetrix "Gene Chip", the Applied Microarrays "CodeLink" arrays, and the Eppendorf "DualChip & Silverquant". One strength of the single-dye system lies in the fact that an aberrant sample cannot affect the raw data derived from other samples, because each array chip is exposed to only one sample (as opposed to a two-color system in which a single low-quality sample may drastically impinge on overall data precision even if the other sample was of high quality). Another benefit is that data are more easily compared to arrays from different experiments; the absolute values of gene expression may be compared between studies conducted months or years apart. A drawback to the one-color system is that, when compared to the two-color system, twice as many microarrays are needed to compare samples within an experiment.

Microarrays and bioinformatics

The advent of inexpensive microarray experiments created several specific bioinformatics challenges:

- the multiple levels of replication in experimental design (Experimental design)
- the number of platforms and independent groups and data format (Standardization)
- the treatment of the data (Statistical analysis)
- accuracy and precision (Relation between probe and gene)
- the sheer volume of data and the ability to share it (Data warehousing)



Gene expression values from microarray experiments can be represented as heat maps to visualize the result of data analysis.

Experimental design

Due to the biological complexity of gene expression, the considerations of experimental design that are discussed in the expression profiling article are of critical importance if statistically and biologically valid conclusions are to be drawn from the data.

There are three main elements to consider when designing a microarray experiment. First, replication of the biological samples is essential for drawing conclusions from the experiment. Second, technical replicates (two RNA samples obtained from each experimental unit) help to ensure precision and allow for testing differences within treatment groups. The technical replicates may be two independent RNA extractions or two aliquots of the same extraction. Third, spots of each cDNA clone or oligonucleotide are present as replicates (at least duplicates) on the microarray slide, to provide a measure of technical precision in each hybridization. It is critical that information about the sample preparation and handling is discussed, in order to help identify the independent units in the experiment and to avoid inflated estimates of statistical significance.[15]

Standardization

Microarray data is difficult to exchange due to the lack of standardization in platform fabrication, assay protocols, and analysis methods. This presents an interoperability problem in bioinformatics. Various grass-roots open-source projects are trying to ease the exchange and analysis of data produced with non-proprietary chips:

- For example, the "Minimum Information About a Microarray Experiment" (MIAME) checklist helps define the level of detail that should exist and is being adopted by many journals as a requirement for the submission of papers incorporating microarray results. But MIAME does not describe the format for the information, so while many formats can support the MIAME requirements, as of 2007 no format permits verification of complete semantic compliance.
- The "MicroArray Quality Control (MAQC) Project" is being conducted by the US Food and Drug Administration (FDA) to develop standards and quality control metrics which will eventually allow the use of MicroArray data in drug discovery, clinical practice and regulatory decision-making.[16]

- The MGED Society has developed standards for the representation of gene expression experiment results and relevant annotations.

Statistical analysis

The analysis of DNA microarrays poses a large number of statistical problems, including the normalization of the data. There are several normalization methods in the published literature some of which are platform specific; as in many other cases where authorities disagree, a sound conservative approach is to directly compare different normalization methods to determine the effects of these different methods on the results obtained. This can be done, for example, by investigating the performance of various methods on data from "spike-in" experiments.

Also, experimenters must account for multiple comparisons: even if the statistical P-value assigned to a gene indicates that it is extremely unlikely that differential expression of this gene was due to random rather than treatment effects, the very high number of genes on an array makes it likely that differential expression of some genes represent false positives or false negatives. Statistical methods tailored to microarray analyses have recently become available that assess statistical power based on the variation present in the data and the number of experimental replicates, and can help minimize type I and type II errors in the analyses.[17]

A basic difference between microarray data analysis and much traditional biomedical research is the dimensionality of the data. A large clinical study might collect 100 data items per patient for thousands of patients. A medium-size microarray study will obtain many thousands of numbers per sample for perhaps a hundred samples. Many analysis techniques treat each sample as a single point in a space with thousands of dimensions, then attempt by various techniques to reduce the dimensionality of the data to something humans can visualize.[18] An example for such a method is the Local Pooled Error (LPE) test, which pools standard deviations of genes with similar expression levels and thereby overcomes the problem of low replicate numbers.[19]

Relation between probe and gene

The relation between a probe and the mRNA that it is expected to detect is problematic. On the one hand, some mRNAs may cross-hybridize probes in the array that are supposed to detect another mRNA. On the other hand, probes that are designed to detect the mRNA of a particular gene may be relying on genomic EST information that is incorrectly associated with that gene.

Data warehousing

Microarray data was found to be more useful when compared to other similar datasets. The sheer volume (in bytes), specialized formats (such as MIAME), and curation efforts associated with the datasets require specialized databases to store the data.

See also

- Systems biology
- Microfluidics or lab-on-chip
- Cyanine dyes, such as Cy3 and Cy5, are commonly used fluorophores with microarrays
- Serial analysis of gene expression
- Significance analysis of microarrays
- Full Genome Sequencing

References

[1] Kulesh DA, Clive DR, Zarlenga DS, Greene JJ (1987). "Identification of interferon-modulated proliferation-related cDNA sequences". *Proc Natl Acad Sci USA* **84**: 8453–8457. doi: 10.1073/pnas.84.23.8453 (http://dx.doi.org/10.1073/pnas.84.23.8453). PMID 2446323.

[2] Schena M, Shalon D, Davis RW, Brown PO (1995). "Quantitative monitoring of gene expression patterns with a complementary DNA microarray". *Science* **270**: 467–470. doi: 10.1126/science.270.5235.467 (http://dx.doi.org/10.1126/science.270.5235.467). PMID 7569999.

[3] Lashkari DA, DeRisi JL, McCusker JH, Namath AF, Gentile C, Hwang SY, Brown PO, Davis RW (1997). "Yeast microarrays for genome wide parallel genetic and gene expression analysis". *Proc Natl Acad Sci USA* **94**: 13057–13062. doi: 10.1073/pnas.94.24.13057 (http://dx.doi.org/10.1073/pnas.94.24.13057). PMID 9371799.

[4] Adomas A, Heller G, Olson A, Osborne J, Karlsson M, Nahalkova J, Van Zyl L, Sederoff R, Stenlid J, Finlay R, Asiegbu FO (2008). "Comparative analysis of transcript abundance in Pinus sylvestris after challenge with a saprotrophic, pathogenic or mutualistic fungus". *Tree Physiol*. **28**: 885–897. PMID 18381269.

[5] Pollack JR, Perou CM, Alizadeh AA, Eisen MB, Pergamenschikov A, Williams CF, Jeffrey SS, Botstein D, Brown PO (1999). "Genome-wide analysis of DNA copy-number changes using cDNA microarrays". *Nat Genet* **23**: 41–46. doi: 10.1038/14385 (http://dx.doi.org/10.1038/14385). PMID 10471496.

[6] Moran G, Stokes C, Thewes S, Hube B, Coleman DC, Sullivan D (2004). "Comparative genomics using Candida albicans DNA microarrays reveals absence and divergence of virulence-associated genes in Candida dubliniensis". *Microbiology* **150**: 3363–3382. doi: 10.1099/mic.0.27221-0 (http://dx.doi.org/10.1099/mic.0.27221-0). PMID 15470115.

[7] http://bgmo.jrc.ec.europa.eu/home/docs.htm

[8] Hacia JG, Fan JB, Ryder O, Jin L, Edgemon K, Ghandour G, Mayer RA, Sun B, Hsie L, Robbins CM, Brody LC, Wang D, Lander ES, Lipshutz R, Fodor SP, Collins FS (1999). "Determination of ancestral alleles for human single-nucleotide polymorphisms using high-density oligonucleotide arrays". *Nat Genet* **22**: 164-167. doi: 10.1038/9674 (http://dx.doi.org/10.1038/9674). PMID 10369258.

[9] Lausted C et al. (2004). " POSaM: a fast, flexible, open-source, inkjet oligonucleotide synthesizer and microarrayer (http://genomebiology.com/2004/5/8/R58)". *Genome Biology* **5**: R58. doi: 10.1186/gb-2004-5-8-r58 (http://dx.doi.org/10.1186/gb-2004-5-8-r58). PMID 15287980. .

[10] Bammler T, Beyer RP, Bhattacharya S, Boorman GA, Boyles A, Bradford BU, Bumgarner RE, Bushel PR, Chaturvedi K, Choi D, Cunningham ML, Deng S, Dressman HK, Fannin RD, Farin FM, Freedman JH, Fry RC, Harper A, Humble MC, Hurban P, Kavanagh TJ, Kaufmann WK, Kerr KF, Jing L, Lapidus JA, Lasarev MR, Li J, Li YJ, Lobenhofer EK, Lu X, Malek RL, Milton S, Nagalla SR, O'malley JP, Palmer VS, Pattee P, Paules RS, Perou CM, Phillips K, Qin LX, Qiu Y, Quigley SD, Rodland M, Rusyn I, Samson LD, Schwartz DA, Shi Y, Shin JL, Sieber SO, Slifer S, Speer MC, Spencer PS, Sproles DI, Swenberg JA, Suk WA, Sullivan RC, Tian R, Tennant RW, Todd SA, Tucker CJ, Van Houten B, Weis BK, Xuan S, Zarbl H; Members of the Toxicogenomics Research Consortium. (2005). "Standardizing global gene expression analysis between laboratories and across platforms". *Nat Methods* **2**: 351–356. doi: 10.1038/nmeth0605-477a (http://dx.doi.org/10.1038/nmeth0605-477a). PMID 15846362.

[11] Pease AC, Solas D, Sullivan EJ, Cronin MT, Holmes CP, Fodor SP. (1994). "Light-generated oligonucleotide arrays for rapid DNA sequence analysis". *PNAS* **91**: 5022–5026. doi: 10.1073/pnas.91.11.5022 (http://dx.doi.

org/10.1073/pnas.91.11.5022). PMID 8197176.
[12] Nuwaysir EF, Huang W, Albert TJ, Singh J, Nuwaysir K, Pitas A, Richmond T, Gorski T, Berg JP, Ballin J, McCormick M, Norton J, Pollock T, Sumwalt T, Butcher L, Porter D, Molla M, Hall C, Blattner F, Sussman MR, Wallace RL, Cerrina F, Green RD. (2002). "Gene expression analysis using oligonucleotide arrays produced by maskless photolithography". *Genome Res* **12**: 1749–1755. doi: 10.1101/gr.362402 (http://dx.doi.org/10.1101/gr.362402). PMID 12421762.
[13] Shalon D, Smith SJ, Brown PO (1996). "A DNA microarray system for analyzing complex DNA samples using two-color fluorescent probe hybridization". *Genome Res* **6**: 639–645. doi: 10.1101/gr.6.7.639 (http://dx.doi.org/10.1101/gr.6.7.639). PMID 8796352.
[14] Tang T, François N, Glatigny A, Agier N, Mucchielli MH, Aggerbeck L, Delacroix H (2007). "Expression ratio evaluation in two-colour microarray experiments is significantly improved by correcting image misalignment". *Bioinformatics* **23**: 2686–2691. doi: 10.1093/bioinformatics/btm399 (http://dx.doi.org/10.1093/bioinformatics/btm399). PMID 17698492.
[15] Churchill GA (2002). " Fundamentals of experimental design for cDNA microarrays (http://www.vmrf.org/research-websites/gcf/Forms/Churchill.pdf)" (– Scholar search (http://scholar.google.co.uk/scholar?hl=en&lr=&q=intitle:Fundamentals+of+experimental+design+for+cDNA+microarrays&as_publication=Nature+genetics+suppliment&as_ylo=2002&as_yhi=2002&btnG=Search)). *Nature genetics suppliment* **32**: 490. doi: 10.1038/ng1031 (http://dx.doi.org/10.1038/ng1031). .
[16] NCTR Center for Toxicoinformatics - MAQC Project (http://www.fda.gov/nctr/science/centers/toxicoinformatics/maqc/)
[17] Wei C, Li J, Bumgarner RE. (2004). "Sample size for detecting differentially expressed genes in microarray experiments". *BMC Genomics* **5**: 87. doi: 10.1186/1471-2164-5-87 (http://dx.doi.org/10.1186/1471-2164-5-87). PMID 15533245.
[18] Wouters L, Gõhlmann HW, Bijnens L, Kass SU, Molenberghs G, Lewi PJ (2003). "Graphical exploration of gene expression data: a comparative study of three multivariate methods". *Biometrics* **59**: 1131–1139. doi: 10.1111/j.0006-341X.2003.00130.x (http://dx.doi.org/10.1111/j.0006-341X.2003.00130.x).
[19] Jain N, Thatte J, Braciale T, Ley K, O'Connell M, Lee JK (2003). "Local-pooled-error test for identifying differentially expressed genes with a small number of replicated microarrays". *Bioinformatics* **19**: 1945–1951. doi: 10.1093/bioinformatics/btg264 (http://dx.doi.org/10.1093/bioinformatics/btg264).

Glossary

- An **Array** or **slide** is a collection of *features* spatially arranged in a two dimensional grid, arranged in columns and rows.
- **Block** or **subarray**: a group of spots, typically made in one print round; several subarrays/blocks form an array.
- **Case/control**: an experimental design paradigm especially suited to the two-colour array system, in which a condition chosen as control (such as healthy tissue or state) is compared to an altered condition (such as a diseased tissue or state).
- **Channel**: the fluorescence output recorded in the scanner for an individual fluorophore and can even be ultraviolet.
- **Dye flip** or **Dye swap** or **Fluor reversal**: reciprocal labelling of DNA targets with the two dyes to account for dye bias in experiments.
- **Scanner**: an instrument used to detect and quantify the intensity of fluorescence of spots on a microarray slide, by selectively exciting fluorophores with a laser and measuring the fluorescence with a filter (optics) photomultiplier system.
- **Spot** or **feature**: a small area on an array slide that contains picomoles of specific DNA samples.
- For other relevant terms see:

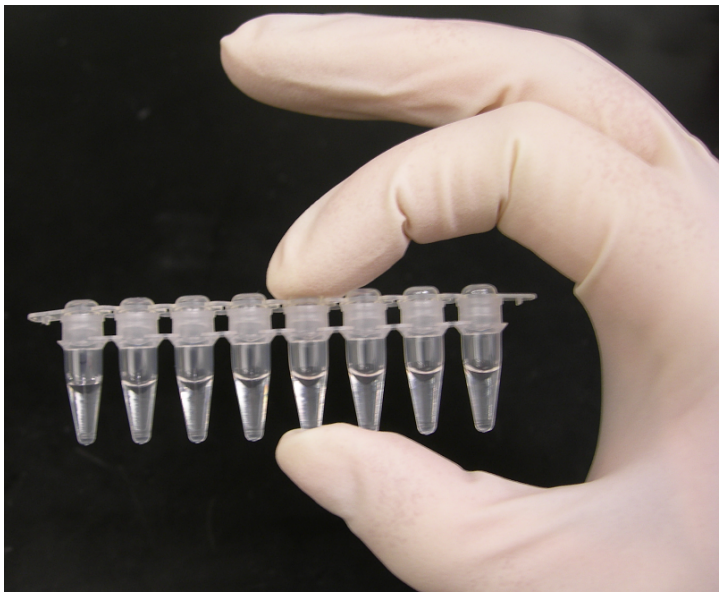
  Glossary of gene expression terms

  Protocol (natural sciences)

External links

- Many important links can be found at the Open Directory Project
  - Gene Expression (http://www.dmoz.org/Science/Biology/Biochemistry_and_Molecular_Biology/Gene_Expression/) at the Open Directory Project
  - Micro Scale Products and Services for Biochemistry and Molecular Biology (http://www.dmoz.org/Science/Biology/Biochemistry_and_Molecular_Biology/Products_and_Services/Micro_Scale/) at the Open Directory Project
  - Products and Services for Gene Expression (http://www.dmoz.org/Science/Biology/Biochemistry_and_Molecular_Biology/Gene_Expression/Products_and_Services/) at the Open Directory Project
- PLoS Biology Primer: Microarray Analysis (http://biology.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pbio.0000015)
- Rundown of microarray technology (http://www.genome.gov/page.cfm?pageID=10000533)
- ArrayMining.net (http://www.arraymining.net) - a free web-server for online microarray analysis
- CLASSIFI (http://pathcuric1.swmed.edu/pathdb/classifi.html) - Gene Ontology-based gene cluster classification resource
- Microarray - How does it work? (http://www.unsolvedmysteries.oregonstate.edu/microarray_07)
- Microarray data processing using Self-Organizing Maps tutorial: Part 1 (http://blog.peltarion.com/2007/04/10/the-self-organized-gene-part-1) Part 2 (http://blog.peltarion.com/2007/06/13/the-self-organized-gene-part-2)

Polymerase chain reaction



A strip of eight PCR tubes, each containing a 100µl reaction.

In molecular biology, the **polymerase chain reaction** (**PCR**) is a technique to amplify a single or few copies of a piece of → DNA across several orders of magnitude, generating millions or more copies of a particular DNA sequence. The method relies on thermal cycling, consisting of cycles of repeated heating and cooling of the reaction for DNA melting and enzymatic replication of the DNA. Primers (short DNA fragments) containing sequences complementary to the target region along with a DNA polymerase (after which the method is named) are key components to enable selective and repeated amplification. As PCR progresses, the DNA generated is itself used as a template for replication, setting in motion a chain reaction in which the DNA template is exponentially amplified. PCR can be extensively modified to perform a wide array of genetic manipulations.

Almost all PCR applications employ a heat-stable DNA polymerase, such as Taq polymerase, an enzyme originally isolated from the bacterium *Thermus aquaticus*. This DNA polymerase enzymatically assembles a new DNA strand from DNA building blocks, the nucleotides, by using single-stranded DNA as a template and DNA oligonucleotides (also called DNA primers), which are required for initiation of DNA synthesis. The vast majority of PCR methods use thermal cycling, i.e., alternately heating and cooling the PCR sample to a defined series of temperature steps. These thermal cycling steps are necessary to physically separate the strands (at high temperatures) in a DNA double helix (DNA melting) used as the template during DNA synthesis (at lower temperatures) by the DNA polymerase to selectively amplify the target DNA. The selectivity of PCR results from the use of primers that are complementary to the DNA region targeted for amplification under specific thermal cycling conditions.

Developed in 1984 by Kary Mullis,[1] PCR is now a common and often indispensable technique used in medical and biological research labs for a variety of applications.[2] [3] These include DNA cloning for sequencing, DNA-based phylogeny, or functional analysis of genes; the diagnosis of hereditary diseases; the identification of genetic fingerprints (used in forensic sciences and paternity testing); and the detection and diagnosis of infectious diseases. In 1993 Mullis was awarded the Nobel Prize in Chemistry for his work on PCR.[4]

PCR principles and procedure

PCR is used to amplify specific regions of a DNA strand (the DNA target). This can be a single gene, a part of a gene, or a non-coding sequence. Most PCR methods typically amplify DNA fragments of up to 10 kilo base pairs (kb), although some techniques allow for amplification of fragments up to 40 kb in size.[5]

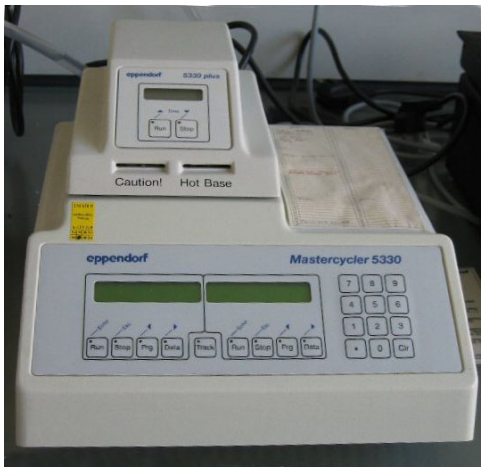


Figure 1a: An old thermal cycler for PCR

A basic PCR set up requires several components and reagents.[6] These components include:

- *DNA template* that contains the DNA region (target) to be amplified.
- Two *primers* that are complementary to the 3' (three prime) ends of each of the sense and anti-sense strand of the DNA target.
- *Taq polymerase* or another DNA polymerase with a temperature optimum at around 70°C.
- *Deoxynucleoside triphosphates* (dNTPs; also very commonly and erroneously called deoxynucleotide triphosphates), the building blocks from which the DNA polymerases synthesizes a new DNA strand.
- *Buffer solution,* providing a suitable chemical environment for optimum activity and stability of the DNA polymerase.
- *Divalent cations,* magnesium or manganese ions; generally Mg^{2+} is used, but Mn^{2+} can be utilized for PCR-mediated DNA mutagenesis, as higher Mn^{2+} concentration increases the error rate during DNA synthesis[7]
- *Monovalent cation* potassium ions.

Figure 1b: An older model three-temperature thermal cycler for PCR

The PCR is commonly carried out in a reaction volume of 10-200 µl in small reaction tubes (0.2-0.5 ml volumes) in a thermal cycler. The thermal cycler heats and cools the reaction tubes to achieve the temperatures required at each step of the reaction (see below). Many modern thermal cyclers make use of the Peltier effect which permits both heating and cooling of the block holding the PCR tubes simply by reversing the electric current. Thin-walled reaction tubes permit favorable thermal conductivity to allow for rapid thermal equilibration. Most thermal cyclers have heated lids to prevent condensation at the top of the reaction tube. Older thermocyclers lacking a heated lid require a layer of oil on top of the reaction mixture or a ball of wax inside the tube.

Procedure

The PCR usually consists of a series of 20 to 40 repeated temperature changes called cycles; each cycle typically consists of 2-3 discrete temperature steps. Most commonly PCR is carried out with cycles that have three temperature steps (Fig. 2). The cycling is often preceded by a single temperature step (called *hold*) at a high temperature (>90°C), and followed by one hold at the end for final product extension or brief storage. The temperatures used and the length of time they are applied in each cycle depend on a variety of parameters. These include the enzyme used for DNA synthesis, the concentration of divalent ions and dNTPs in the reaction, and the melting temperature (Tm) of the primers.[8]

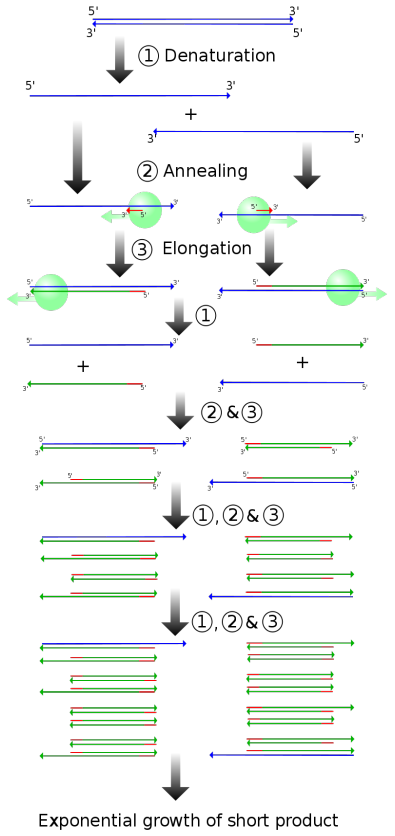


Figure 2: Schematic drawing of the PCR cycle. **(1) Denaturing at 94–96°C. (2) Annealing at ~65°C (3) Elongation at 72°C**. Four cycles are shown here. The blue lines represent the DNA template to which primers (red arrows) anneal that are extended by the DNA polymerase (light green circles), to give shorter DNA products (green lines), which themselves are used as templates as PCR progresses.

- *Initialization step*: This step consists of heating the reaction to a temperature of 94–96°C (or 98°C if extremely thermostable polymerases are used), which is held for 1–9 minutes. It is only required for DNA polymerases that require heat activation by hot-start PCR.[9]
- *Denaturation step*: This step is the first regular cycling event and consists of heating the reaction to 94–98°C for 20–30 seconds. It causes melting of DNA template and primers by disrupting the hydrogen bonds between complementary bases of the DNA strands, yielding single strands of DNA.
- *Annealing step*: The reaction temperature is lowered to 50–65°C for 20–40 seconds allowing annealing of the primers to the single-stranded DNA template. Typically the annealing temperature is about 3-5 degrees Celsius below the Tm of the primers used. Stable DNA-DNA hydrogen bonds are only formed when the primer sequence very closely matches the template sequence. The polymerase binds to the primer-template hybrid and begins DNA synthesis.
- *Extension/elongation step*: The temperature at this step depends on the DNA polymerase used; Taq polymerase has its optimum activity temperature at 75–80°C,[10] [11] and commonly a temperature of 72°C is used with this enzyme. At this step the DNA polymerase synthesizes a new DNA strand complementary to the DNA template strand by adding dNTPs that are complementary to the template in 5' to 3' direction, condensing the 5'-phosphate group of the dNTPs with the 3'-hydroxyl group at the end of the nascent (extending) DNA strand. The extension time depends both on the DNA polymerase used and on the length of the DNA fragment to be amplified. As a rule-of-thumb, at its optimum temperature, the DNA polymerase will polymerize a thousand bases per minute. Under optimum conditions, i.e., if there are no limitations due to limiting substrates or

reagents, at each extension step, the amount of DNA target is doubled, leading to exponential (geometric) amplification of the specific DNA fragment.

- *Final elongation*: This single step is occasionally performed at a temperature of 70–74°C for 5–15 minutes after the last PCR cycle to ensure that any remaining single-stranded DNA is fully extended.
- *Final hold*: This step at 4–15°C for an indefinite time may be employed for short-term storage of the reaction.

To check whether the PCR generated the anticipated DNA fragment (also sometimes referred to as the amplimer or amplicon), agarose gel electrophoresis is employed for size separation of the PCR products. The size(s) of PCR products is determined by comparison with a DNA ladder (a molecular weight marker), which contains DNA fragments of known size, run on the gel alongside the PCR products (see Fig. 3).

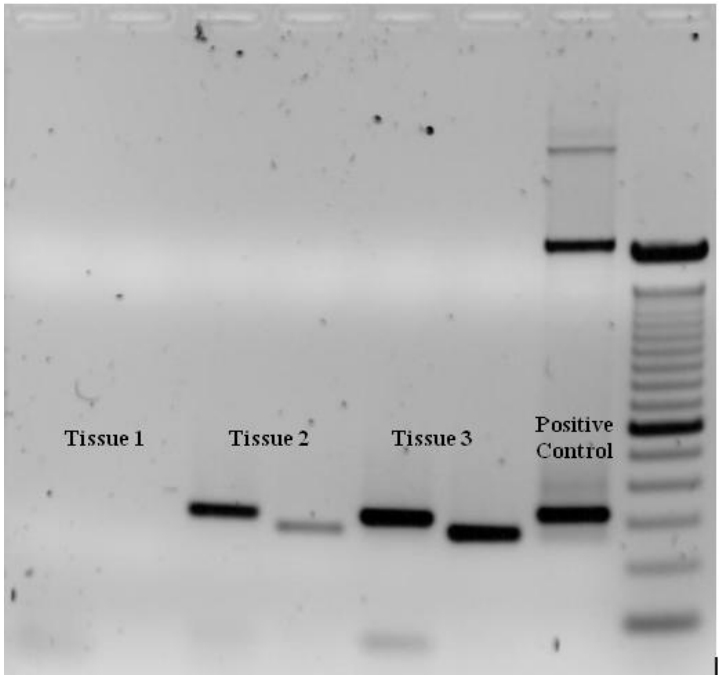


Figure 3: Ethidium bromide-stained PCR products after gel electrophoresis. Two sets of primers were used to amplify a target sequence from three different tissue samples. No amplification is present in sample #1; DNA bands in sample #2 and #3 indicate successful amplification of the target sequence. The gel also shows a positive control, and a DNA ladder containing DNA fragments of defined length for sizing the bands in the experimental PCRs.

PCR stages

The PCR process can be divided into three stages:

Exponential amplification: At every cycle, the amount of product is doubled (assuming 100% reaction efficiency). The reaction is very sensitive: only minute quantities of DNA need to be present.[12]

Levelling off stage: The reaction slows as the DNA polymerase loses activity and as consumption of reagents such as dNTPs and primers causes them to become limiting.

Plateau: No more product accumulates due to exhaustion of reagents and enzyme.

PCR optimization

In practice, PCR can fail for various reasons, in part due to its sensitivity to contamination causing amplification of spurious DNA products. Because of this, a number of techniques and procedures have been developed for optimizing PCR conditions.[13] [14] Contamination with extraneous DNA is addressed with lab protocols and procedures that separate pre-PCR mixtures from potential DNA contaminants.[6] This usually involves spatial separation of PCR-setup areas from areas for analysis or purification of PCR products, and thoroughly cleaning the work surface between reaction setups. Primer-design techniques are important in improving PCR product yield and in avoiding the formation of spurious products, and the

usage of alternate buffer components or polymerase enzymes can help with amplification of long or otherwise problematic regions of DNA.

Application of PCR

Isolation of genomic DNA

PCR allows isolation of DNA fragments from genomic DNA by selective amplification of a specific region of DNA. This use of PCR augments many methods, such as generating hybridization probes for Southern or northern hybridization and DNA cloning, which require larger amounts of DNA, representing a specific DNA region. PCR supplies these techniques with high amounts of pure DNA, enabling analysis of DNA samples even from very small amounts of starting material.

Other applications of PCR include DNA sequencing to determine unknown PCR-amplified sequences in which one of the amplification primers may be used in Sanger sequencing, isolation of a DNA sequence to expedite recombinant DNA technologies involving the insertion of a DNA sequence into a plasmid or the genetic material of another organism. Bacterial colonies (E.coli) can be rapidly screened by PCR for correct DNA vector constructs[15] . PCR may also be used for genetic fingerprinting; a forensic technique used to identify a person or organism by comparing experimental DNAs through different PCR-based methods.

Some PCR 'fingerprints' methods have high discriminative power and can be used to identify genetic relationships between individuals, such as parent-child or between siblings, and are used in paternity testing (Fig. 4). This technique may also be used to determine evolutionary relationships among organisms.

Amplification and quantitation of DNA

Because PCR amplifies the regions of DNA that it targets, PCR can be used to analyze extremely small amounts of sample. This is often critical for forensic analysis, when only a trace amount of DNA is available as evidence. PCR may also be used in the analysis of ancient DNA that is tens of thousands of years old. These PCR-based techniques have been successfully used on animals, such as a forty-thousand-year-old mammoth, and also on human DNA, in applications ranging from the analysis of Egyptian mummies to the identification of a Russian Tsar.[16]

Quantitative PCR methods allow the estimation of the amount of a given sequence present in a sample – a technique often applied to quantitatively determine levels of gene expression. Real-time PCR is an established tool for DNA quantification that measures the accumulation of DNA product after each round of PCR amplification.

- See also Use of DNA in forensic entomology

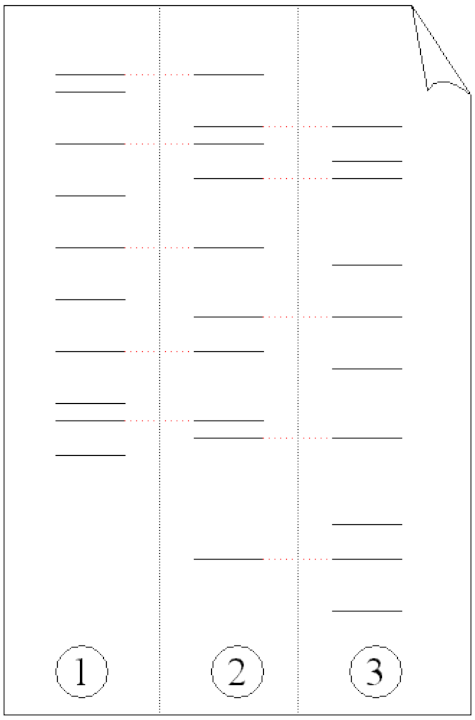


Figure 4: Electrophoresis of PCR-amplified DNA fragments. (1) Father. (2) Child. (3) Mother. The child has inherited some, but not all of the fingerprint of each of its parents, giving it a new, unique fingerprint.

PCR in diagnosis of diseases

PCR allows early diagnosis of malignant diseases such as leukemia and lymphomas, which is currently the highest developed in cancer research and is already being used routinely. PCR assays can be performed directly on genomic DNA samples to detect translocation-specific malignant cells at a sensitivity which is at least 10,000 fold higher than other methods.

PCR also permits identification of non-cultivatable or slow-growing microorganisms such as mycobacteria, anaerobic bacteria, or viruses from tissue culture assays and animal models. The basis for PCR diagnostic applications in microbiology is the detection of infectious agents and the discrimination of non-pathogenic from pathogenic strains by virtue of specific genes.

Viral DNA can likewise be detected by PCR. The primers used need to be specific to the targeted sequences in the DNA of a virus, and the PCR can be used for diagnostic analyses or DNA sequencing of the viral genome. The high sensitivity of PCR permits virus detection soon after infection and even before the onset of disease. Such early detection may give physicians a significant lead in treatment. The amount of virus ("viral load") in a patient can also be quantified by PCR-based DNA quantitation techniques (see below).

Variations on the basic PCR technique

- **Allele-specific PCR**: This diagnostic or cloning technique is used to identify or utilize single-nucleotide polymorphisms (SNPs) (single base differences in DNA). It requires prior knowledge of a DNA sequence, including differences between alleles, and uses primers whose 3' ends encompass the SNP. PCR amplification under stringent conditions is much less efficient in the presence of a mismatch between template and primer, so successful amplification with an SNP-specific primer signals presence of the specific SNP in a sequence.[17] See SNP genotyping for more information.
- **Assembly PCR** or **Polymerase Cycling Assembly (PCA)**: Assembly PCR is the artificial synthesis of long DNA sequences by performing PCR on a pool of long oligonucleotides with short overlapping segments. The oligonucleotides alternate between sense and antisense directions, and the overlapping segments determine the order of the PCR fragments thereby selectively producing the final long DNA product.[18]
- **Asymmetric PCR**: Asymmetric PCR is used to preferentially amplify one strand of the original → DNA more than the other. It finds use in some types of sequencing and hybridization probing where having only one of the two complementary strands is required. PCR is carried out as usual, but with a great excess of the primers for the chosen strand. Due to the slow (arithmetic) amplification later in the reaction after the limiting primer has been used up, extra cycles of PCR are required.[19] A recent modification on this process, known as **L**inear-**A**fter-**T**he-**E**xponential-PCR (LATE-PCR), uses a limiting primer with a higher melting temperature (Tm) than the excess primer to maintain reaction efficiency as the limiting primer concentration decreases mid-reaction.[20]
- **Helicase-dependent amplification**: This technique is similar to traditional PCR, but uses a constant temperature rather than cycling through denaturation and annealing/extension cycles. DNA Helicase, an enzyme that unwinds DNA, is used in place of thermal denaturation.[21]
- **Hot-start PCR**: This is a technique that reduces non-specific amplification during the initial set up stages of the PCR. The technique may be performed manually by heating the reaction components to the melting temperature (e.g., 95˚C) before adding the polymerase.[22] Specialized enzyme systems have been developed that inhibit the polymerase's activity at ambient temperature, either by the binding of an antibody[9] or by the presence of covalently bound inhibitors that only dissociate after a high-temperature activation step. Hot-start/cold-finish PCR is achieved with new hybrid polymerases that are inactive at ambient temperature and are instantly activated at elongation temperature.
- **Intersequence-specific PCR** (ISSR): a PCR method for DNA fingerprinting that amplifies regions between some simple sequence repeats to produce a unique fingerprint of amplified fragment lengths.[23]
- **Inverse PCR**: a method used to allow PCR when only one internal sequence is known. This is especially useful in identifying flanking sequences to various genomic inserts. This involves a series of DNA digestions and self ligation, resulting in known sequences at either end of the unknown sequence.[24]
- **Ligation-mediated PCR**: This method uses small DNA linkers ligated to the DNA of interest and multiple primers annealing to the DNA linkers; it has been used for DNA

sequencing, genome walking, and DNA footprinting.[25]

- **Methylation-specific PCR** (MSP): The MSP method was developed by Stephen Baylin and Jim Herman at the Johns Hopkins School of Medicine,[26] and is used to detect methylation of CpG islands in genomic DNA. DNA is first treated with sodium bisulfite, which converts unmethylated cytosine bases to uracil, which is recognized by PCR primers as thymine. Two PCRs are then carried out on the modified DNA, using primer sets identical except at any CpG islands within the primer sequences. At these points, one primer set recognizes DNA with cytosines to amplify methylated DNA, and one set recognizes DNA with uracil or thymine to amplify unmethylated DNA. MSP using qPCR can also be performed to obtain quantitative rather than qualitative information about methylation.
- **Miniprimer PCR**: Miniprimer PCR uses a novel thermostable polymerase (S-Tbr) that can extend from short primers ("smalligos") as short as 9 or 10 nucleotides, instead of the approximately 20 nucleotides required by Taq. This method permits PCR targeting smaller primer binding regions, and is particularly useful to amplify unknown, but conserved, DNA sequences, such as the 16S (or eukaryotic 18S) rRNA gene. 16S rRNA miniprimer PCR was used to characterize a microbial mat community growing in an extreme environment, a hypersaline pond in Puerto Rico. In that study, deeply divergent sequences were discovered with high frequency and included representatives that de□ned two new division-level taxa, suggesting that miniprimer PCR may reveal new dimensions of microbial diversity.[27] By enlarging the "sequence space" that may be queried by PCR primers, this technique may enable novel PCR strategies that are not possible within the limits of primer design imposed by Taq and other commonly used enzymes.
- **Multiplex Ligation-dependent Probe Amplification** (**MLPA**): permits multiple targets to be amplified with only a single primer pair, thus avoiding the resolution limitations of multiplex PCR (see below).
- **Multiplex-PCR**: The use of multiple, unique primer sets within a single PCR mixture to produce amplicons of varying sizes specific to different DNA sequences. By targeting multiple genes at once, additional information may be gained from a single test run that otherwise would require several times the reagents and more time to perform. Annealing temperatures for each of the primer sets must be optimized to work correctly within a single reaction, and amplicon sizes, i.e., their base pair length, should be different enough to form distinct bands when visualized by gel electrophoresis.
- **Nested PCR**: increases the specificity of DNA amplification, by reducing background due to non-specific amplification of DNA. Two sets of primers are being used in two successive PCRs. In the first reaction, one pair of primers is used to generate DNA products, which besides the intended target, may still consist of non-specifically amplified DNA fragments. The product(s) are then used in a second PCR with a set of primers whose binding sites are completely or partially different from and located 3' of each of the primers used in the first reaction. Nested PCR is often more successful in specifically amplifying long DNA fragments than conventional PCR, but it requires more detailed knowledge of the target sequences.
- **Overlap-extension PCR**: is a genetic engineering technique allowing the construction of a DNA sequence with an alteration inserted beyond the limit of the longest practical primer length.

- **Quantitative PCR (Q-PCR)**: is used to measure the quantity of a PCR product (preferably real-time). It is the method of choice to quantitatively measure starting amounts of DNA, cDNA or RNA. Q-PCR is commonly used to determine whether a DNA sequence is present in a sample and the number of its copies in the sample. The method with currently the highest level of accuracy is **Quantitative real-time PCR**. It is often confusingly known as RT-PCR (**R**eal **T**ime PCR) or RQ-PCR. QRT-PCR or RTQ-PCR are more appropriate contractions. RT-PCR commonly refers to reverse transcription PCR (see below), which is often used in conjunction with Q-PCR. QRT-PCR methods use fluorescent dyes, such as Sybr Green, or fluorophore-containing DNA probes, such as TaqMan, to measure the amount of amplified product in real time.
- **RT-PCR**: (**R**everse **T**ranscription PCR) is a method used to amplify, isolate or identify a known sequence from a cellular or tissue RNA. The PCR is preceded by a reaction using reverse transcriptase to convert RNA to cDNA. RT-PCR is widely used in expression profiling, to determine the expression of a gene or to identify the sequence of an RNA transcript, including transcription start and termination sites and, if the genomic DNA sequence of a gene is known, to map the location of exons and introns in the gene. The 5' end of a gene (corresponding to the transcription start site) is typically identified by an RT-PCR method, named RACE-PCR, short for *Rapid Amplification of cDNA Ends*.
- **Solid Phase PCR**: encompasses multiple meanings, including Polony Amplification (where PCR colonies are derived in a gel matrix, for example), 'Bridge PCR' (the only primers present are covalently linked to solid support surface), conventional Solid Phase PCR (where Asymmetric PCR is applied in the presence of solid support bearing primer with sequence matching one of the aqueous primers) and Enhanced Solid Phase PCR[28] (where conventional Solid Phase PCR can be improved by employing high Tm and nested solid support primer with optional application of a thermal 'step' to favour solid support priming).
- **TAIL-PCR**: **Thermal asymmetric interlaced** PCR is used to isolate unknown sequence flanking a known sequence. Within the known sequence TAIL-PCR uses a nested pair of primers with differing annealing temperatures; a degenerate primer is used to amplify in the other direction from the unknown sequence.[29]
- **Touchdown PCR**: a variant of PCR that aims to reduce nonspecific background by gradually lowering the annealing temperature as PCR cycling progresses. The annealing temperature at the initial cycles is usually a few degrees (3-5˚C) above the T_m of the primers used, while at the later cycles, it is a few degrees (3-5˚C) below the primer T_m. The higher temperatures give greater specificity for primer binding, and the lower temperatures permit more efficient amplification from the specific products formed during the initial cycles.[30]
- **PAN-AC**: This method uses isothermal conditions for amplification, and may be used in living cells.[31] [32]
- **Universal Fast Walking**: this method allows genome walking and genetic fingerprinting using a more specific 'two-sided' PCR than conventional 'one-sided' approaches (using only one gene-specific primer and one general primer - which can lead to artefactual 'noise') [33] by virtue of a mechanism involving lariat structure formation. Streamlined derivatives of UFW are LaNe RAGE (lariat-dependent nested PCR for rapid amplification of genomic DNA ends) [34] , 5'RACE LaNe [35] and 3'RACE LaNe [36] .

History

A 1971 paper in the Journal of Molecular Biology by Kleppe and co-workers first described a method using an enzymatic assay to replicate a short DNA template with primers *in vitro*.[37] However, this early manifestation of the basic PCR principle did not receive much attention, and the invention of the polymerase chain reaction in 1983 is generally credited to Kary Mullis.[38]

At the core of the PCR method is the use of a suitable DNA polymerase able to withstand the high temperatures of >90°C (>195°F) required for separation of the two DNA strands in the DNA double helix after each replication cycle. The DNA polymerases initially employed for in vitro experiments presaging PCR were unable to withstand these high temperatures.[2] So the early procedures for DNA replication were very inefficient, time consuming, and required large amounts of DNA polymerase and continual handling throughout the process.

The discovery in 1976 of Taq polymerase (a DNA polymerase purified from the thermophilic bacterium, *Thermus aquaticus*, which naturally occurs in hot (50 to 80 °C (120 to 175 °F)) environments[10]) paved the way for dramatic improvements of the PCR method. The DNA polymerase isolated from *T. aquaticus* is stable at high temperatures remaining active even after DNA denaturation,[11] thus obviating the need to add new DNA polymerase after each cycle[3] . This allowed an automated thermocycler-based process for DNA amplification.

When Mullis developed the PCR in 1983, he was working in Emeryville, California for Cetus Corporation, one of the first biotechnology companies. There, he was responsible for synthesizing short chains of DNA. Mullis has written that he conceived of PCR while cruising along the Pacific Coast Highway one night in his car.[39] He was playing in his mind with a new way of analyzing changes (mutations) in DNA when he realized that he had instead invented a method of amplifying any DNA region through repeated cycles of duplication driven by DNA polymerase.

In *Scientific American*, Mullis summarized the procedure: "Beginning with a single molecule of the genetic material DNA, the PCR can generate 100 billion similar molecules in an afternoon. The reaction is easy to execute. It requires no more than a test tube, a few simple reagents, and a source of heat."[40] He was awarded the Nobel Prize in Chemistry in 1993 for his invention,[4] seven years after he and his colleagues at Cetus first put his proposal to practice. However, some controversies have remained about the intellectual and practical contributions of other scientists to Mullis' work, and whether he had been the sole inventor of the PCR principle. (see main article: Kary Mullis)

Patent wars

The PCR technique was patented by Kary Mullis and assigned to Cetus Corporation, where Mullis worked when he invented the technique in 1983. The *Taq* polymerase enzyme was also covered by patents. There have been several high-profile lawsuits related to the technique, including an unsuccessful lawsuit brought by DuPont. The pharmaceutical company Hoffmann-La Roche purchased the rights to the patents in 1992 and currently holds those that are still protected.

A related patent battle over the Taq polymerase enzyme is still ongoing in several jurisdictions around the world between Roche and Promega. The legal arguments have extended beyond the lives of the original PCR and Taq polymerase patents, which expired on March 28, 2005[41]

References

[1] Bartlett & Stirling (2003)—A Short History of the Polymerase Chain Reaction. In: Methods Mol Biol. 226:3-6 (http://www.springerprotocols.com/Abstract/doi/10.1385/1-59259-384-4:3)

[2] Saiki, RK; Scharf S, Faloona F, Mullis KB, Horn GT, Erlich HA, Arnheim N (December 20 1985). " Enzymatic amplification of beta-globin genomic sequences and restriction site analysis for diagnosis of sickle cell anemia (http://sunsite.berkeley.edu/cgi-bin/ebind2html/pcr/034)". *Science* **230** (4732): 1350–4. doi: 10.1126/science.2999980 (http://dx.doi.org/10.1126/science.2999980). PMID 2999980. .

[3] Saiki, RK; Gelfand DH, Stoffel S, Scharf SJ, Higuchi R, Horn GT, Mullis KB, Erlich HA (1988). " Primer-directed enzymatic amplification of DNA with a thermostable DNA polymerase (http://sunsite.berkeley.edu/cgi-bin/ebind2html/pcr/009)". *Science* **239**: 487–91. doi: 10.1126/science.2448875 (http://dx.doi.org/10.1126/science.2448875). PMID 2448875. .

[4] Karry Mullis Nobel Lecture, December 8, 1993 (http://nobelprize.org/nobel_prizes/chemistry/laureates/1993/mullis-lecture.html)

[5] Cheng S, Fockler C, Barnes WM, Higuchi R (1994). "Effective amplification of long targets from cloned inserts and human genomic DNA". *Proc Natl Acad Sci.* **91**: 5695–5699. doi: 10.1073/pnas.91.12.5695 (http://dx.doi.org/10.1073/pnas.91.12.5695). PMID 8202550.

[6] Joseph Sambrook and David W. Russel (2001). *Molecular Cloning: A Laboratory Manual* (3rd ed.). Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory Press. ISBN 0-87969-576-5. Chapter 8: In vitro Amplification of DNA by the Polymerase Chain Reaction

[7] Pavlov AR, Pavlova NV, Kozyavkin SA, Slesarev AI (2004). "Recent developments in the optimization of thermostable DNA polymerases for efficient applications". *Trends Biotechnol.* **22**: 253–260. doi: 10.1016/j.tibtech.2004.02.011 (http://dx.doi.org/10.1016/j.tibtech.2004.02.011). PMID 15109812.

[8] Rychlik W, Spencer WJ, Rhoads RE (1990). " Optimization of the annealing temperature for DNA amplification *in vitro* (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=2243783)". *Nucl Acids Res* **18**: 6409–6412. doi: 10.1093/nar/18.21.6409 (http://dx.doi.org/10.1093/nar/18.21.6409). PMID 2243783. .

[9] D.J. Sharkey, E.R. Scalice, K.G. Christy Jr., S.M. Atwood, and J.L. Daiss (1994). "Antibodies as Thermolabile Switches: High Temperature Triggering for the Polymerase Chain Reaction". *Bio/Technology* **12**: 506–509. doi: 10.1038/nbt0594-506 (http://dx.doi.org/10.1038/nbt0594-506).

[10] Chien A, Edgar DB, Trela JM (1976). "Deoxyribonucleic acid polymerase from the extreme thermophile Thermus aquaticus". *J. Bacteriol* **174**: 1550–1557. PMID 8432.

[11] Lawyer FC, Stoffel S, Saiki RK, Chang SY, Landre PA, Abramson RD, Gelfand DH (1993). "High-level expression, purification, and enzymatic characterization of full-length Thermus aquaticus DNA polymerase and a truncated form deficient in 5' to 3' exonuclease activity". *PCR Methods Appl.* **2**: 275–287. PMID 8324500.

[12] Campbell Biology,7th edition

[13] PCR from problematic templates. Focus 22:1 p.10 (2000).

[14] Helpful tips for PCR. Focus 22:1 p.12 (2000).

[15] Pavlov AR, Pavlova NV, Kozyavkin SA, Slesarev AI (2006). "Thermostable DNA Polymerases for a Wide Spectrum of Applications: Comparison of a Robust Hybrid TopoTaq to other enzymes". in Kieleczawa J. *DNA Sequencing II: Optimizing Preparation and Cleanup*. Jones and Bartlett. pp. 241–257. ISBN 0-7637-3383-0.

[16] "Chemical Synthesis, Sequencing, and Amplification of DNA (class notes on MBB/BIO 343)" (http://photoscience.la.asu.edu/photosyn/courses/BIO_343/lecture/DNAtech.html). Arizona State University. . Retrieved on 2007-10-29.

[17] Newton CR, Graham A, Heptinstall LE, Powell SJ, Summers C, Kalsheker N, Smith JC, and Markham AF (1989). "Analysis of any point mutation in DNA. The amplification refractory mutation system (ARMS)". *Nucleic Acids Research* **17** (7): 2503–2516. doi: 10.1093/nar/17.7.2503 (http://dx.doi.org/10.1093/nar/17.7.2503). PMID 2785681.

[18] Stemmer WP, Crameri A, Ha KD, Brennan TM, Heyneker HL (1995). "Single-step assembly of a gene and entire plasmid from large numbers of oligodeoxyribonucleotides". *Gene* **164**: 49–53. doi: 10.1016/0378-1119(95)00511-4 (http://dx.doi.org/10.1016/0378-1119(95)00511-4). PMID 7590320.

[19] Innis MA, Myambo KB, Gelfand DH, Brow MA. (1988). "DNA sequencing with Thermus aquaticus DNA polymerase and direct sequencing of polymerase chain reaction-amplified DNA". *Proc Natl Acad Sci USA* **85**: 9436–4940. doi: 10.1073/pnas.85.24.9436 (http://dx.doi.org/10.1073/pnas.85.24.9436). PMID 3200828.

[20] Pierce KE and Wangh LJ (2007). "Linear-after-the-exponential polymerase chain reaction and allied technologies Real-time detection strategies for rapid, reliable diagnosis from single cells". *Methods Mol Med.* **132**: 65–85. doi: 10.1007/978-1-59745-298-4_7 (http://dx.doi.org/10.1007/978-1-59745-298-4_7). PMID 17876077.

[21] Myriam Vincent, Yan Xu and Huimin Kong (2004). "Helicase-dependent isothermal DNA amplification". *EMBO reports* **5** (8): 795–800. doi: 10.1038/sj.embor.7400200 (http://dx.doi.org/10.1038/sj.embor.7400200).

[22] Q. Chou, M. Russell, D.E. Birch, J. Raymond and W. Bloch (1992). "Prevention of pre-PCR mis-priming and primer dimerization improves low-copy-number amplifications". *Nucleic Acids Research* **20**: 1717–1723. doi: 10.1093/nar/20.7.1717 (http://dx.doi.org/10.1093/nar/20.7.1717). PMID 1579465.

[23] E. Zietkiewicz, A. Rafalski, and D. Labuda (1994). "Genome fingerprinting by simple sequence repeat (SSR)-anchored polymerase chain reaction amplification". *Genomics* **20** (2): 176–83. doi: 10.1006/geno.1994.1151 (http://dx.doi.org/10.1006/geno.1994.1151).

[24] Ochman H, Gerber AS, Hartl DL (1988). "Genetic applications of an inverse polymerase chain reaction". *Genetics* **120**: 621–623. PMID 2852134.

[25] Mueller PR, Wold B (1988). "*In vivo* footprinting of a muscle specific enhancer by ligation mediated PCR". *Science* **246**: 780–786. doi: 10.1126/science.2814500 (http://dx.doi.org/10.1126/science.2814500). PMID 2814500.

[26] Herman JG, Graff JR, Myöhänen S, Nelkin BD, Baylin SB (1996). "Methylation-specific PCR: a novel PCR assay for methylation status of CpG islands". *Proc Natl Acad Sci USA* **93** (13): 9821–9826. doi: 10.1073/pnas.93.18.9821 (http://dx.doi.org/10.1073/pnas.93.18.9821). PMID 8790415.

[27] Isenbarger TA, Finney M, Ríos-Velázquez C, Handelsman J, Ruvkun G (2008). "Miniprimer PCR, a new lens for viewing the microbial world". *Applied and Environmental Microbiology* **74**: 840–9. doi: 10.1128/AEM.01933-07 (http://dx.doi.org/10.1128/AEM.01933-07). PMID 18083877.

[28] Khan Z, Poetter K, Park DJ (2008). "Enhanced solid phase PCR: mechanisms to increase priming by solid support primers". *Analytical Biochemistry* **375**: 391–393. doi: 10.1016/j.ab.2008.01.021 (http://dx.doi.org/10.1016/j.ab.2008.01.021). PMID 18267099.

[29] Y.G. Liu and R. F. Whittier (1995). "Thermal asymmetric interlaced PCR: automatable amplification and sequencing of insert end fragments from P1 and YAC clones for chromosome walking". *Genomics* **25** (3): 674–81. doi: 10.1016/0888-7543(95)80010-J (http://dx.doi.org/10.1016/0888-7543(95)80010-J).

[30] Don RH, Cox PT, Wainwright BJ, Baker K, Mattick JS (1991). " 'Touchdown' PCR to circumvent spurious priming during gene amplification (http://www.pubmedcentral.nih.gov/pagerender.fcgi?artid=328507&pageindex=1)". *Nucl Acids Res* **19**: 4008. doi: 10.1093/nar/19.14.4008 (http://dx.doi.org/10.1093/nar/19.14.4008). PMID 1861999. .

[31] David, F.Turlotte, E., (1998). "An Isothermal Amplification Method". *C.R.Acad. Sci Paris, Life Science* **321** (1): 909–914.

[32] Fabrice David (September-October 2002). "Utiliser les propriétés topologiques de l'ADN: une nouvelle arme contre les agents pathogènes" (http://www.lab-rech-associatives.com/pdf/Utiliser la Topologie de l'ADN.pdf) (PDF). Fusion. .(in French)

[33] Myrick KV, Gelbart WM (2002). "Universal Fast Walking for direct and versatile determination of flanking sequence". *Gene* **284**: 125–131. doi: 10.1016/S0378-1119(02)00384-0 (http://dx.doi.org/10.1016/S0378-1119(02)00384-0). PMID 11891053.

[34] Park DJ Electronic Journal of Biotechnology (online). 15 August 2005, vol. 8, no. 2 (http://www.ejbiotechnology.info/content/vol8/issue2/full/7/index.html)

[35] Park DJ (2005). "A new 5' terminal murine GAPDH exon identified using 5'RACE LaNe". *Molecular Biotechnology* **29**: 39–46. doi: 10.1385/MB:29:1:39 (http://dx.doi.org/10.1385/MB:29:1:39). PMID 15668518.

[36] Park DJ (2004). "3'RACE LaNe: a simple and rapid fully nested PCR method to determine 3'-terminal cDNA sequence". *Biotechniques* **36**: 586–588,590. PMID 15088375.

[37] Kleppe K, Ohtsuka E, Kleppe R, Molineux I, Khorana HG (1971). " Studies on polynucleotides. XCVI. Repair replications of short synthetic DNA's as catalyzed by DNA polymerases (http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6WK7-4DKM9WR-36&_user=103681&_coverDate=03/14/1971&_rdoc=10&_fmt=summary&_orig=browse&_srch=doc-info(#toc#6899#1971#999439997#524037#FLA#display#Volume)&_cdi=6899&_sort=d&_docanchor=&view=c&_ct=18&_acct=C000007920&_version=1&_urlVersion=0&_userid=103681&md5=5e1e29e72e51ebd62d1b60d1bd5f9058)". *J. Mol. Biol.* **56**: 341–361. doi: 10.1016/0022-2836(71)90469-4 (http://dx.doi.org/10.1016/0022-2836(71)90469-4). .

[38] Rabinow, Paul (1996). *Making PCR: A Story of Biotechnology*. Chicago: University of Chicago Press. ISBN 0-226-70146-8.

[39] Mullis, Kary (1998). *Dancing Naked in the Mind Field*. New York: Pantheon Books. ISBN 0-679-44255-3.

[40] Mullis, Kary (1990). "The unusual origin of the polymerase chain reaction". *Scientific American* **262** (4): 56–61, 64–5.

[41] Advice on How to Survive the Taq Wars ¶2 (http://www.genengnews.com/articles/chitem.aspx?aid=1656&chid=0): GEN Genetic Engineering News Biobusiness Channel: Article. May 1 2006 (Vol. 26, No. 9).

External links

- PCR Virtual Lab (http://learn.genetics.utah.edu/content/labs/pcr/)
- US Patent for PCR (http://patft.uspto.gov/netacgi/nph-Parser?Sect2=PTO1&Sect2=HITOFF&p=1&u=/netahtml/PTO/search-bool.html&r=1&f=G&l=50&d=PALL&RefSrch=yes&Query=PN/4683202)
- Step-through animation of PCR (http://www.dnalc.org/ddnalc/resources/pcr.html) - Cold Spring Harbor Laboratory Adobe Flash required
- PCR at Home (http://www.sciam.com/article.cfm?articleID=00035C6C-229B-1C74-9B81809EC588EF21) - performing PCRs with low-cost household materials Scientific American

Transcriptome

The **transcriptome** is the set of all messenger RNA (mRNA) molecules, or "transcripts," produced in one or a population of cells. The term can be applied to the total set of transcripts in a given organism, or to the specific subset of transcripts present in a particular cell type. Unlike the genome, which is roughly fixed for a given cell line (excluding mutations), the transcriptome can vary with external environmental conditions. Because it includes all *mRNA* transcripts in the cell, the transcriptome reflects the genes that are being actively expressed at any given time, with the exception of mRNA degradation phenomena such as transcriptional attenuation. The study of *transcriptomics*, also referred to as Expression Profiling, examines the expression level of mRNAs in a given cell population, often using high-throughput techniques based on → DNA microarray technology. The use of next-generation sequencing technology to study the transcriptome at the nucleotide level is known as RNA-Seq [1].

Transcriptomics is that branch of chemistry,which deals with the study of messenger RNA molecules produced in one or a population of cell type.

Applications and analysis

The transcriptomes of stem cells and cancer cells are of particular interest to researchers who seek to understand the processes of cellular differentiation and carcinogenesis. A number of organism-specific transcriptome databases have been constructed and annotated to aid in the identification of genes that are differentially expressed in distinct cell populations or subtypes; however, the analysis of relative mRNA expression levels can be complicated by the fact that relatively small changes in mRNA expression can produce large changes in the total amount of the corresponding protein present in the cell. One analysis method, known as Gene Set Enrichment Analysis, identifies coregulated gene networks rather than individual genes that are up- or down-regulated in different cell populations[2].

mRNA regulation

Although microarray studies can reveal the relative amounts of different mRNAs in the cell, levels of mRNA are not directly proportional to the expression level of the proteins they code for. The number of protein molecules synthesized using a given mRNA molecule as a template is highly dependent on translation-initiation features of the mRNA sequence; in particular, the ability of the translation initiation sequence is a key determinant in the recruiting of ribosomes for protein translation. The complete protein complement of a cell or organism is known as the proteome.

A study of 158,807 mouse transcripts revealed that 4520 of these transcripts form antisense partners that are base pair complementary to the exons of genes[3]. These results raise the possibility that significant numbers of "antisense RNA-coding genes" might participate in the regulation of the levels of expression of protein-coding mRNAs.

References

1. ^ Wang Z, Gerstein M, Snyder M. (2009). RNA-Seq: a revolutionary tool for transcriptomics. *Nature Rev. Genetics* 10(1): 57-63.
2. ^ Subramanian A, Tamayo P, Mootha VK, Mukherjee S, Ebert BL, Gillette MA, Paulovich A, Pomeroy SL, Golub TR, Lander ES, Mesirov JP. (2005). Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. *Proc Natl Acad Sci USA* 102(43):15545-50.
3. ^ "**Antisense Transcription in the Mammalian Transcriptome**" by the RIKEN Genome Exploration Research Group and Genome Science Group (Genome Network Project Core Group) and the FANTOM Consortium: S. Katayama et al. in *Science, Vol 309, Issue 5740, 1564-1566 , 2 September 2005.*
4. ^ Velculescu VE, Zhang L, Zhou W, Vogelstein J, Basrai MA, Bassett DE Jr, Hieter P, Vogelstein B, Kinzler KW. Characterization of the yeast transcriptome. Cell. 1997 Jan 24;88(2):243-51.
5. ^ Laule O, Hirsch-Hoffmann M, Hruz T, Gruissem W, and P Zimmermann. (2006) Web-based analysis of the mouse transcriptome using Genevestigator. BMC Bioinformatics 7:311

See also

- Expression profiling
- List of omics topics in biology
- Bioinformatics
- → DNA microarrays (a.k.a. DNA chips)
- Gene expression
- Serial analysis of gene expression
- RNA-Seq
- Metabolomics
- Genevestigator
- Proteome

References

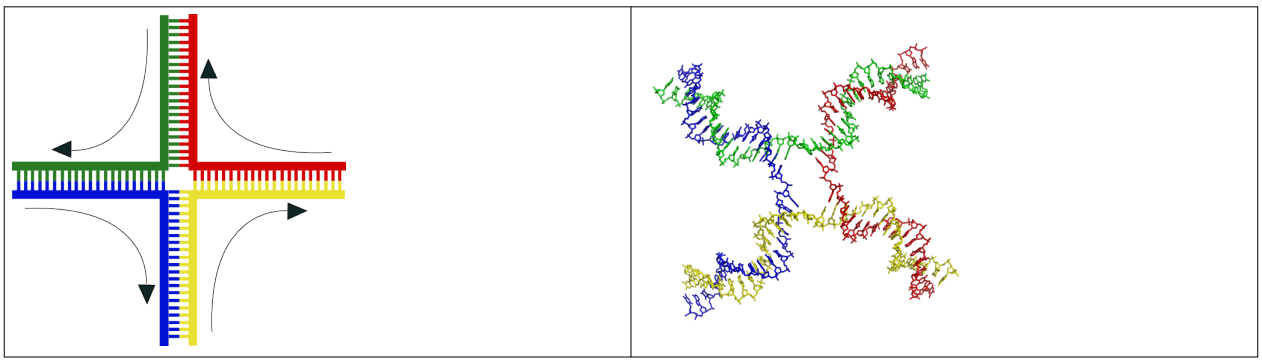
[1] http://en.wikipedia.org/wiki/Transcriptome#endnote_Wang
[2] http://en.wikipedia.org/wiki/Transcriptome#endnote_Subramanian
[3] http://en.wikipedia.org/wiki/Transcriptome#endnote_antisense

DNA nanotechnology

Part of a series of articles on **Molecular self-assembly**
Self-assembled monolayer Supramolecular assembly → DNA nanotechnology
See also Nanotechnology

DNA nanotechnology is a subfield of nanotechnology which seeks to use the unique molecular recognition properties of → DNA and other nucleic acids to create novel, controllable structures out of DNA. The DNA is thus used as a structural material rather than as a carrier of genetic information, making it an example of bionanotechnology. This has possible applications in molecular self-assembly and in DNA computing.

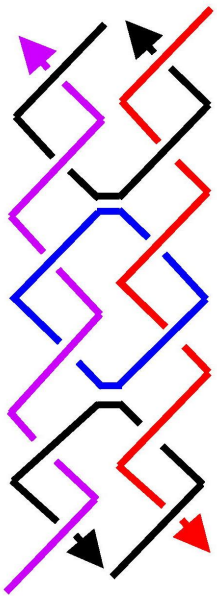
Introduction: DNA crossover molecules



Structure of the 4-arm junction.
Left: A schematic. **Right**: A more realistic model.[1]
Each of the four separate DNA single strands are shown in different colors.

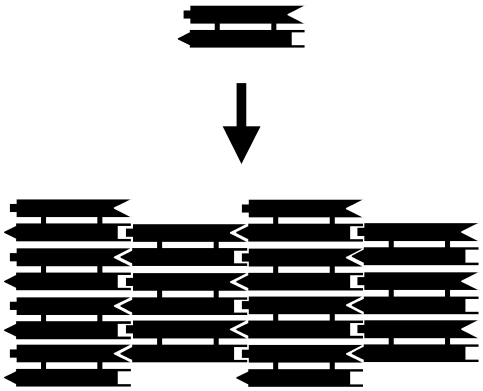
DNA nanotechnology makes use of branched DNA structures to create DNA complexes with useful properties. → DNA is normally a linear molecule, in that its axis is unbranched. However, DNA molecules containing junctions can also be made. For example, a four-arm junction can be made using four individual DNA strands which are complementary to each other in the correct pattern. Due to Watson-Crick base pairing, only portions of the strands which are complementary to each other will attach to each other to form duplex DNA. This four-arm junction is an immobile form of a Holliday junction.

Junctions can be used in more complex molecules. The most important of these is the "double-crossover" or DX motif. Here, two DNA duplexes lie next to each other, and share two junction points where strands cross from one duplex into the other. This molecule has the advantage that the junction points are now constrained to a single orientation as opposed to being flexible as in the four-arm junction. This makes the DX motif suitible as a structural building block for larger DNA complexes.[3]



A double-crossover (DX) molecule. This molecule consists of five → DNA single strands which form two double-helical domains, on the left and the right in this image. There are two crossover points where the strands cross from one domain into the other. Image from Mao, 2004. [2]

Tile-based arrays



Assembly of a DX array. Each bar represents a double-helical domain of → DNA, with the shapes representing comlimentary sticky ends. The DX molecule at top will combine into the two-dimensional DNA array shown at bottom. Image from Mao, 2004. [4]

DX arrays

DX, Double Crossover, molecules can be equipped with sticky ends in order to combine them into a two-dimenstional periodic lattice. Each DX molecule has four termini, one at each end of the two double-helical domains, and these can be equipped with sticky ends that program them to combine into a specific pattern. More than one type of DX can be used which can be made to arrange in rows or any other tessellated pattern. They thus form extended flat sheets which are essentially two-dimensional crystals of DNA.[5]

DNA nanotubes

In addition to flat sheets, DX arrays have been made to form hollow tubes of 4-20 nm diameter. These DNA nanotubes are somewhat similar in size and shape to carbon nanotubes, but the carbon nanotubes are stronger and better conductors, whereas the DNA nanotubes are more easily modified and connected to other structures.[6]

Other tile arrays

Two-dimensional arrays have been made out of other motifs as well, including the Holliday junction rhombus array as well as various DX-based arrays in the shapes of triangles and hexagons.[7] Another motif, the six-helix bundle, has the ability to form three-dimensional DNA arrays as well.[8]

DNA origami

As an alternative to the tile-based approach, two-dimensional DNA structures can be made from a single, long DNA strand of arbitrary sequence which is folded into the desired shape by using shorter, "staple" strands. This allows the creation of two-dimensional shapes at the nanoscale using → DNA. Demonstrated designs have included the smiley face and a coarse map of North America. DNA origami was the cover story of *Nature* on March 15, 2006.[9]

DNA polyhedra

A number of three-dimensional DNA molecules have been made which have the connectivity of a polyhedron such as an octahedron or cube. In other words, the DNA duplexes trace the edges of a polyhedron with a DNA junction at each vertex. The earliest demonstrations of DNA polyhedra involved multiple ligations and solid-phase synthesis steps to create catenated polyhedra. More recently, there have been demonstrations of a DNA truncated octahedron made from a long single strand designed to fold into the correct conformation, as well as a tetrahedron which can be produced from four DNA strands in a single step.[10]

DNA nanomechanical devices

DNA complexes have been made which change their conformation upon some stimulus. These are intended to have applications in nanorobotics. One of the first such devices, called "molecular tweezers," changes from an open to a closed state based upon the presence of control strands.

DNA machines have also been made which show a twisting motion. One of these makes use of the transition between the B-DNA and Z-DNA forms to respond to a change in buffer conditions. Another relies on the presence of control strands to switch from a paranemic-crossover (PX) conformation to a double-junction (JX2) conformation.[11]

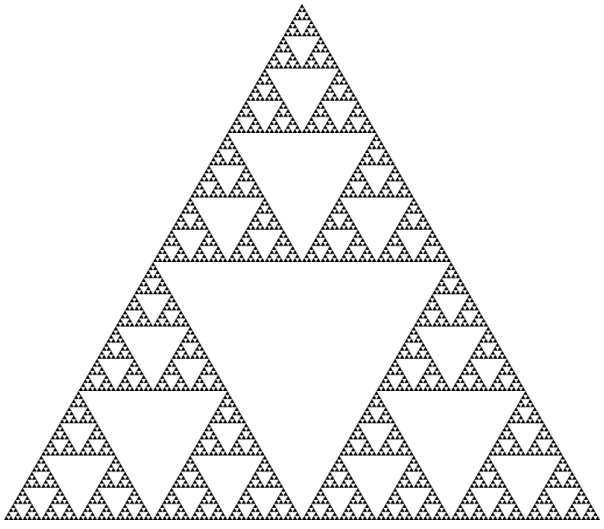
Stem Loop Controllers

A design called a *stem loop*, consisting of a single strand of DNA which has a loop at an end, are a dynamic structure that opens and closes when a piece of DNA bonds to the loop part. This effect has been exploited to create several logic gates. [12] [13] These logic gates have been used to create the computers MAYA I and MAYA II which can play tick-tac-toe to some extent.[14]

Applications

Algorithmic self-assembly

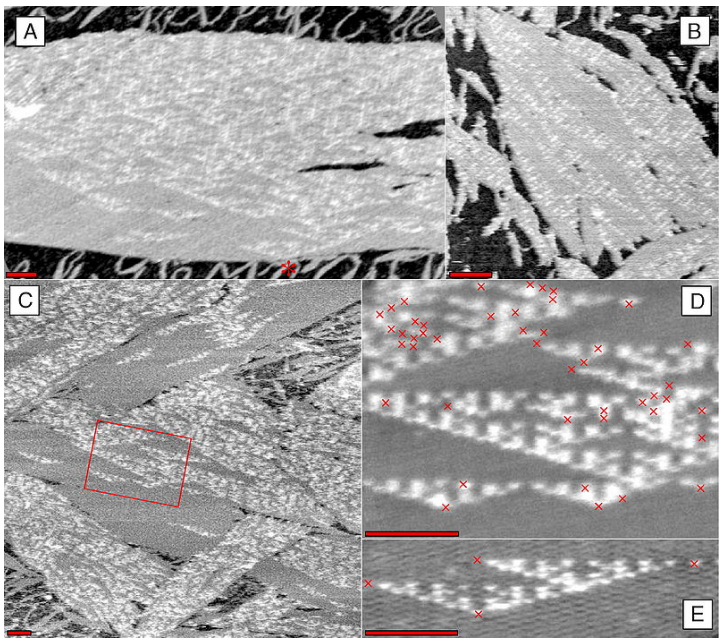
DNA nanotechnology has been applied to the related field of DNA computing. A DX array has been demonstrated whose assembly encodes an XOR operation, which allows the DNA array to implement a cellular automaton which generates a fractal called the Sierpinski gasket. This shows that computation can be incorporated into the assembly of DNA arrays, increasing its scope beyond simple periodic arrays.



The Sierpinski gasket.

Note that DNA computing overlaps with, but is distinct from, DNA nanotechnology. The latter uses the specificity of Watson-Crick basepairing to make novel structures out of DNA. These structures can be used for DNA computing, but they do not have to be. Additionally, DNA computing can be done without using the types of molecules made possible by DNA Nanotechnology.[16]

Nanoarchitecture



DNA arrays that display a representation of the Sierpinski gasket on their surfaces. Click the image for further details. Image from Rothemund *et al.*, 2004. [15]

The idea of using DNA arrays to template the assembly of other functional molecules has been around for a while, but only recently has progress been made in reducing these kinds of schemes to practice. In 2006, researchers covalently attached gold nanoparticles to a DX-based tile and showed that self-assembly of the DNA structures also assembled the nanoparticles hosted on them. A non-covalent hosting scheme was shown in 2007, using Dervan polyamides on a DX array to arrange streptavidin proteins on specific kinds of tiles on the DNA array.[17] Previously in 2006 LaBean demonstrated the letters "D" "N" and "A" created on a 4x4 DX array using streptavidin. [18]

DNA has also been used to assemble a single walled carbon nanotube Field-effect_transistor.[19]

See also

- Mechanical properties of DNA

External links

- Chengde Mao page at Purdue University [20]
- John Reif lab at Duke University [21]
- Nadrian Seeman lab at NYU [22]
- William M. Shih lab at Harvard Medical School [23]
- Andrew Turberfield lab at Oxford University [24]
- Erik Winfree lab at Caltech [25]
- Hao Yan lab at Arizona State University [26]
- Bernard Yurke formerly at Bell Labs [27] now at Boise State University [28]
- Thom LaBean at Duke University [29]
- Software for 3D DNA design, modeling and/or simulation:
  - Ascalaph Designer [30]
  - caDNAno [31]
  - GIDEON [32]
  - NanoEngineer-1 [33]
- International Society for Nanoscale Science, Computation and Engineering [34]

References

Note: Click on the doi to access the text of the referenced article.

[1] Created from PDB 1M6G (http://www.rcsb.org/pdb/explore/explore.do?structureId=1M6G)

[2] http://dx.doi.org/10.1371/journal.pbio.0020431

- Seeman, Nadrian C. (1 November 1999). "DNA Engineering and its Application to Nanotechnology". *Trends in Biotechnology* **17** (11): 437–443. doi: 10.1016/S0167-7799(99)01360-8 (http://dx.doi.org/10.1016/S0167-7799(99)01360-8). ISSN 0167-7799 (http://worldcat.org/issn/0167-7799).
- Seeman, Nadrian C. (January 2001). "DNA Nicks and Nodes and Nanotechnology". *Nano Letters* **1** (1): 22–26. doi: 10.1021/nl000182v (http://dx.doi.org/10.1021/nl000182v). ISSN 1530-6984 (http://worldcat.org/issn/1530-6984).
- Mao, Chengde (December 2004). "The Emergence of Complexity: Lessons from DNA". *PLoS Biology* **2** (12): 2036–2038. doi: 10.1371/journal.pbio.0020431 (http://dx.doi.org/10.1371/journal.pbio.0020431). ISSN 1544-9173 (http://worldcat.org/issn/1544-9173).
- Kumara, Mudalige T. (July 2008). "Assembly pathway analysis of DNA nanostructures and the construction of parallel motifs". *Nano Letters* **8** (7): 1971–1977. doi: 10.1021/nl800907y (http://dx.doi.org/10.1021/nl800907y). ISSN .

[4] http://dx.doi.org/10.1371/journal.pbio.0020431

- Winfree, Erik; Liu, Furong; Wenzler, Lisa A. & Seeman, Nadrian C. (6 August 1998). "Design and self-assembly of two-dimensional DNA crystals". *Nature* **394**: 529–544. doi: 10.1038/28998 (http://dx.doi.org/10.1038/28998). ISSN 0028-0836 (http://worldcat.org/issn/0028-0836).
- Liu, Furong; Sha, Ruojie & Seeman, Nadrian C. (10 February 1999). "Modifying the Surface Features of Two-Dimensional DNA Crystals". *Journal of the American Chemical Society* **121** (5): 917–922. doi: 10.1021/ja982824a (http://dx.doi.org/10.1021/ja982824a). ISSN 0002-7863 (http://worldcat.org/issn/0002-7863).
- Rothemund, Paul W. K.; Ekani-Nkodo, Axel; Papadakis, Nick; Kumar, Ashish; Fygenson, Deborah Kuchnir & Winfree, Erik (22 December 2004). "Design and Characterization of Programmable DNA Nanotubes". *Journal of the American Chemical Society* **126** (50): 16344–16352. doi: 10.1021/ja044319l (http://dx.doi.org/10.1021/ja044319l). ISSN 0002-7863 (http://worldcat.org/issn/0002-7863).
- Mao, Chengde; Sun, Weiqiong & Seeman, Nadrian C. (16 June 1999). "Designed Two-Dimensional DNA Holliday Junction Arrays Visualized by Atomic Force Microscopy". *Journal of the American Chemical Society* **121** (23): 5437–5443. doi: 10.1021/ja9900398 (http://dx.doi.org/10.1021/ja9900398). ISSN 0002-7863 (http://worldcat.org/issn/0002-7863).
- Constantinou, Pamela E.; Wang, Tong; Kopatsch, Jens; Israel, Lisa B.; Zhang, Xiaoping; Ding, Baoquan; Sherman, William B.; Wang, Xing; Zheng, Jianping; Sha, Ruojie & Seeman, Nadrian C. (2006). "Double cohesion in structural DNA nanotechnology". *Organic and Biomolecular Chemistry* **4**: 3414–3419. doi: 10.1039/b605212f (http://dx.doi.org/10.1039/b605212f).
- Mathieu, Frederick; Liao, Shiping; Kopatsch, Jens; Wang, Tong; Mao, Chengde & Seeman, Nadrian C. (April 2005). "Six-Helix Bundles Designed from DNA". *Nano Letters* **5** (4): 661–665. doi: 10.1021/nl050084f (http://dx.doi.org/10.1021/nl050084f). ISSN 1530-6984 (http://worldcat.org/issn/1530-6984).
- Rothemund, Paul W. K. (2006). "Folding DNA to create nanoscale shapes and patterns". *Nature* **440**: 297–302. doi: 10.1038/nature04586 (http://dx.doi.org/10.1038/nature04586). ISSN 0028-0836 (http://worldcat.org/issn/0028-0836).
- Zhang, Yuwen; Seeman, Nadrian C. (1994). "Construction of a DNA-truncated octahedron". *Journal of the American Chemical Society* **116** (5): 1661–1669. doi: 10.1021/ja00084a006 (http://dx.doi.org/10.1021/ja00084a006). ISSN 0002-7863 (http://worldcat.org/issn/0002-7863).
- Shih, William M.; Quispe, Joel D.; Joyce, Gerald F. (12 February 2004). "A 1.7-kilobase single-stranded DNA that folds into a nanoscale octahedron". *Nature* **427**: 618–621. doi: 10.1038/nature02307 (http://dx.doi.org/10.1038/nature02307). ISSN 0028-0836 (http://worldcat.org/issn/0028-0836).
- Goodman, R.P.; Schaap, I.A.T.; Tardin, C.F.; Erben, C.M.; Berry, R.M.; Schmidt, C.F.; Turberfield, A.J. (9 December 2005). "Rapid chiral assembly of rigid DNA building blocks for molecular nanofabrication". *Science* **310** (5754): 1661–1665. doi: 10.1126/science.1120367 (http://dx.doi.org/10.1126/science.1120367). ISSN 0036-8075 (http://worldcat.org/issn/0036-8075).
- Yurke, Bernard; Turberfield, Andrew J.; Mills, Allen P., Jr; Simmel, Friedrich C. & Neumann, Jennifer L. (10 August 2000). "A DNA-fuelled molecular machine made of DNA". *Nature* **406**: 605–609. doi:

10.1038/35020524 (http://dx.doi.org/10.1038/35020524). ISSN 0028-0836 (http://worldcat.org/issn/0028-0836).

- Mao, Chengde; Sun, Weiqiong; Shen, Zhiyong & Seeman, Nadrian C. (14 January 1999). "A DNA Nanomechanical Device Based on the B-Z Transition". *Nature* **397**: 144–146. doi: 10.1038/16437 (http://dx.doi.org/10.1038/16437). ISSN .
- Yan, Hao; Zhang, Xiaoping; Shen, Zhiyong & Seeman, Nadrian C. (3 January 2002). "A robust DNA mechanical device controlled by hybridization topology". *Nature* **415**: 62–65. doi: 10.1038/415062a (http://dx.doi.org/10.1038/415062a). ISSN .

[12] DNA Logic Gates (https://digamma.cs.unm.edu/wiki/bin/view/McogPublicWeb/MolecularLogicGates)
[13] (http://www.duke.edu/~jme17/Joshua_E._Mendoza-Elias/Research_Ideas.html)
[14] MAYA II (https://digamma.cs.unm.edu/wiki/bin/view/McogPublicWeb/MolecularAutomataMAYAII)
[15] http://dx.doi.org/10.1371/journal.pbio.0020424

- Rothemund, Paul W. K.; Papadakis, Nick & Winfree, Erik (December 2004). "Algorithmic Self-Assembly of DNA Sierpinski Triangles". *PLoS Biology* **2** (12): 2041–2053. doi: 10.1371/journal.pbio.0020424 (http://dx.doi.org/10.1371/journal.pbio.0020424). ISSN 1544-9173 (http://worldcat.org/issn/1544-9173).
- Robinson, Bruche H.; Seeman, Nadrian C. (August 1987). "The Design of a Biochip: A Self-Assembling Molecular-Scale Memory Device". *Protein Engineering* **1** (4): 295–300. ISSN 0269-2139 (http://worldcat.org/issn/0269-2139). Link (http://peds.oxfordjournals.org/cgi/content/abstract/1/4/295)
- Zheng, Jiwen; Constantinou, Pamela E.; Micheel, Christine; Alivisatos, A. Paul; Kiehl, Richard A. & Seeman Nadrian C. (2006). "2D Nanoparticle Arrays Show the Organizational Power of Robust DNA Motifs". *Nano Letters* **6**: 1502–1504. doi: 10.1021/nl060994c (http://dx.doi.org/10.1021/nl060994c). ISSN 1530-6984 (http://worldcat.org/issn/1530-6984).
- Cohen, Justin D.; Sadowski, John P.; Dervan, Peter B. (2007). "Addressing Single Molecules on DNA Nanostructures". *Angewandte Chemie* **46** (42): 7956–7959. doi: 10.1002/anie.200702767 (http://dx.doi.org/10.1002/anie.200702767). ISSN 0570-0833 (http://worldcat.org/issn/0570-0833).

[18] Park, Sung Ha; Sung Ha Park, Constantin Pistol, Sang Jung Ahn, John H. Reif, Alvin R. Lebeck, Chris Dwyer, Thomas H. LaBean (October 2006). " Finite-Size, Fully Addressable DNA Tile Lattices Formed by Hierarchical Assembly Procedures (http://www3.interscience.wiley.com/journal/113390879/abstract)". *Angewandte Chemie* **118** (40): 749–753. doi: 10.1002/ange.200690141 (http://dx.doi.org/10.1002/ange.200690141). ISSN 1521-3757 (http://worldcat.org/issn/1521-3757). .
[19] Keren, K.; Kinneret Keren, Rotem S. Berman, Evgeny Buchstab, Uri Sivan, Erez Braun (November 2003). " DNA-Templated Carbon Nanotube Field-Effect Transistor (http://www.sciencemag.org/cgi/content/abstract/sci;302/5649/1380)". *Science* **302** (6549): 1380–1382. doi: 10.1126/science.1091022 (http://dx.doi.org/10.1126/science.1091022). ISSN 1095-9203 (http://worldcat.org/issn/1095-9203). .
[20] http://www.chem.purdue.edu/people/faculty/faculty.asp?itemID=46
[21] http://www.cs.duke.edu/~reif/BMC/Reif.BMCproject.html
[22] http://seemanlab4.chem.nyu.edu/
[23] http://research2.dfci.harvard.edu/shih/SHIH_LAB/Home.html
[24] http://www.physics.ox.ac.uk/cm/people/turberfield.htm
[25] http://dna.caltech.edu/
[26] http://chemistry.asu.edu/faculty/hao_yan.asp
[27] http://www.bell-labs.com/org/physicalsciences/profiles/yurke.html
[28] http://coen.boisestate.edu/departments/faculty.asp?ID=134
[29] http://www.cs.duke.edu/~thl/
[30] http://www.agilemolecule.com/Ascalaph/Ascalaph_Designer.html
[31] http://cadnano.org
[32] http://www.subirac.com
[33] http://www.nanoengineer-1.net
[34] http://www.isnsce.org/

The Cell Interactome

Interactomics

Interactomics is a discipline at the intersection of bioinformatics and biology that deals with studying both the interactions and the consequences of those interactions between and among proteins, and other molecules within a cell[1] . The network of all such interactions is called the Interactome. Interactomics thus aims to compare such networks of interactions (i.e., interactomes) between and within species in order to find how the traits of such networks are either preserved or varied. From a mathematical, or mathematical biology viewpoint an interactome network is a graph or a category representing the most important interactions pertinent to the normal physiological functions of a cell or organism.

Interactomics is an example of "top-down" systems biology, which takes an overhead, as well as overall, view of a biosystem or organism. Large sets of genome-wide and proteomic data are collected, and correlations between different molecules are inferred. From the data new hypotheses are formulated about feedbacks between these molecules. These hypotheses can then be tested by new experiments[2] .

Through the study of the interaction of all of the molecules in a cell the field looks to gain a deeper understanding of genome function and evolution than just examining an individual genome in isolation[1] . Interactomics goes beyond cellular proteomics in that it not only attempts to characterize the interaction between proteins, but between all molecules in the cell.

Methods of interactomics

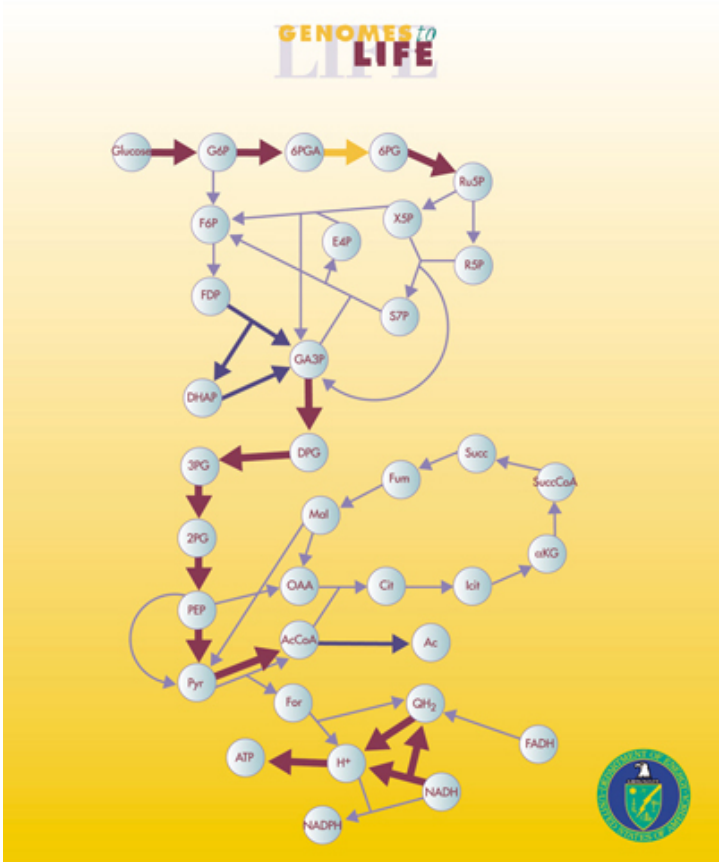
The study of the interactome requires the collection of large amounts of data by way of high throughput experiments. Through these experiments a large number of data points are collected from a single organism under a small number of perturbations[2] These experiments include:

- Two-hybrid screening
- Tandem Affinity Purification
- X-ray tomography
- Optical fluorescence microscopy

Recent developments

The field of interactomics is currently rapidly expanding and developing. While no biological interactomes have been fully characterized. Over 90% of proteins in *Saccharomyces cerevisiae* have been screened and their interactions characterized, making it the first interactome to be nearly fully specified [3] .

Also there have been recent systematic attempts to explore the human interactome[1] and [4] .



Metabolic Network Model for Escherichia coli.

Other species whose interactomes have been studied in some detail include *Caenorhabditis elegans* and *Drosophila melanogaster*.

Criticisms and concerns

Kiemer and Cesareni[1] raise the following concerns with the current state of the field:

- The experimental procedures associated with the field are error prone leading to "noisy results". This leads to 30% of all reported interactions being artifacts. In fact, two groups using the same techniques on the same organism found less than 30% interactions in common.
- Techniques may be biased, i.e. the technique determines which interactions are found.
- Ineractomes are not nearly complete with perhaps the exception of *S. cerivisiae*.
- While genomes are stable, interactomes may vary between tissues and developmental stages.

- Genomics compares amino acids, and nucleotides which are in a sense unchangeable, but interactomics compares proteins and other molecules which are subject to mutation and evolution.
- It is difficult to match evolutionarily related proteins in distantly related species.

See also

- Interaction network
- Proteomics
- Metabolic network
- Metabolic network modelling
- Metabolic pathway
- Genomics
- Mathematical biology
- Systems biology

References

[1] Kiemer, L; G Cesareni (2007). "Comparative interactomics: comparing apples and pears?". *TRENDS in Biochemistry* **25**: 448–454. doi: 10.1016/j.tibtech.2007.08.002 (http://dx.doi.org/10.1016/j.tibtech.2007.08.002).

[2] Bruggeman, F J; H V Westerhoff (2006). "The nature of systems biology". *TRENDS in Microbiology* **15**: 45–50. doi: 10.1016/j.tim.2006.11.003 (http://dx.doi.org/10.1016/j.tim.2006.11.003).

[3] Krogan, NJ; et al. (2006). "Global landscape of protein complexes in the yeast *Saccharomyeses Cerivisiae* ". *Nature* **440**: 637–643. doi: 10.1038/nature04670 (http://dx.doi.org/10.1038/nature04670).

[4] further citation needed

External links

- Interactomics.org (http://interactomics.org). A dedicated interactomics web site operated under BioLicense.
- Interactome.org (http://interactome.org). An interactome wiki site.
- PSIbase (http://psibase.kobic.re.kr) Structural Interactome Map of all Proteins.
- Omics.org (http://omics.org). An omics portal site that is openfree (under BioLicense)
- Genomics.org (http://genomics.org). A Genomics wiki site.
- Comparative Interactomics analysis of protein family interaction networks using PSIMAP (protein structural interactome map) (http://bioinformatics.oxfordjournals.org/cgi/content/full/21/15/3234)
- Interaction interfaces in proteins via the Voronoi diagram of atoms (http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6TYR-4KXVD30-2&_user=10&_coverDate=11/30/2006&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=8361bf3fe7834b4642cdda3b979de8bb)
- Using convex hulls to extract interaction interfaces from known structures. Panos Dafas, Dan Bolser, Jacek Gomoluch, Jong Park, and Michael Schroeder. Bioinformatics 2004 20: 1486-1490.
- PSIbase: a database of Protein Structural Interactome map (PSIMAP). Sungsam Gong, Giseok Yoon, Insoo Jang Bioinformatics 2005.
- Mapping Protein Family Interactions : Intramolecular and Intermolecular Protein Family Interaction Repertoires in the PDB and Yeast, Jong Park, Michael Lappe & Sarah A.

Teichmann,J.M.B (2001).

- Semantic Systems Biology (http://www.semantic-systems-biology.org)

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